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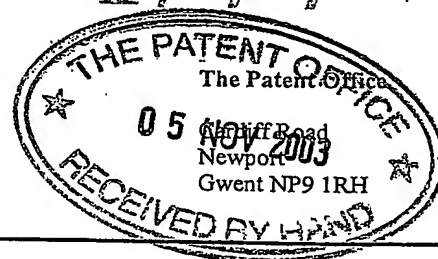
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## Request for grant of a patent

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P035892GB

2. Patent application number

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0325854.8

3. Full name, address and postcode of the or of  
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VERNALIS (CAMBRIDGE) LIMITED  
Granta Park  
Abington  
Cambridge  
CB1 6GB

Patents ADP number (if you know it)

8730947001

If the applicant is a corporate body, give the  
country/state of its incorporation

UNITED KINGDOM

4. Title of the invention

PYRAZOLOPYRIMIDINE COMPOUNDS AND THEIR USE IN  
MEDICINE

5. Name of your agent (if you have one)

CARPMAELS & RANSFORD

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Number of earlier application

Date of filing  
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Abstract

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Request for preliminary examination and search (Patents Form 9/77)

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11. I/We request the grant of a patent on the basis of this application.

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Date

Carpmaels & Ransford

5th November 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

P.N. HOWARD

020-7242 8692

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## Pyrazolopyrimidine Compounds and their Use in Medicine

This invention relates to the use of a class of substituted amino pyrazolo[1,5-a]pyrimidines in relation to diseases which are mediated by excessive or inappropriate kinase activity, for example CDK2 and/or PDK1 and/or CHK1 activity, such as cancers.

### Background to the invention

#### CDK2

Uncontrolled cell proliferation is a hallmark of cancer. Tumor cells typically have damage to genes which play a part in regulation of the cell division cycle. Cyclin-dependent kinases (CDKs) play critical roles in regulating the transitions between different phases of the cell cycle. The serine/threonine kinase CDK2 is essential for normal cell cycling and plays a key role in disorders arising from aberrant cell cycling. Inhibitors of CDK2 are therefore useful for the treatment of various types of cancer and other conditions related to abnormal cell proliferation. Flavopyridol (M.D. Losiewicz et al., Biochem. Biophys. Res. Commun., 1994, 201, 589-595), which is currently in clinical trials, displays modest selectivity for inhibition of CDKs over other kinases but inhibits CDK1, CDK2, and CDK4 with equal potency. A purine based derivative, roscovitine (CYC-202) (W.F. De Azevedo et al., Eur. J. Biochem., 1997, 243, 518-526), similarly displays selectivity for CDKs over other kinases and is also in clinical trials.

#### PDK1

For a normal cell to acquire the phenotype of a malignant tumour cell, several barriers must be overcome. One of the most important is the ability to evade programmed cell death (apoptosis). Mutations downregulating various aspects of the cell-death machinery are therefore a hallmark of cancer. The PI-3 kinase-AKT pathway transmits survival signals from growth factor receptors to downstream effectors. In a substantial number of tumour cells, this pathway is inappropriately activated by either amplification of the PI-3 kinase or Akt genes, or loss of expression of the PTEN tumour suppressor. Activation of this pathway enables cancer cells to survive under conditions

where normal cells would die, enabling the continued expansion of the tumour. The 3'-phosphoinositide-dependent protein kinase-1 (PDK1) is an essential component of the PI-3 kinase-AKT pathway. In the presence of PIP3, the second messenger generated by PI-3 kinase, PDK1 phosphorylates Akt on threonine 308, a modification essential for Akt activation. PDK1 also phosphorylates the corresponding threonine residues of certain other pro-survival kinases including SGK and p70 S6 kinase (Vanhaesebroeck B & Alessi DR. *Biochem J* 346, 561-576 (2000)). Experiments with genetically modified mice indicate that reducing PDK1 activity to 10% of the normal level is surprisingly well tolerated (Lawlor MA et al. *EMBO J* 21, 3728-3738 (2002)). Certain cancer cells, however, appear to be less able to tolerate antisense-mediated reductions in PDK1 activity (Flynn P et al. *Curr Biol.* 10, 1439-1442 (2000)). Moreover, both celecoxib and UCN-01, small molecules that inhibit PDK1 both in vitro and in cells, are capable of inducing apoptosis in cultured tumour cells (Arico et al. *J. Biol. Chem.* 277, 27613-27621 (2002); Sato et al. *Oncogene* 21, 1727-1738 (2002)). Agents that inhibit the PDK1 kinase may therefore be useful for the therapy of cancer.

### CHK1

Many standard cancer chemotherapeutic agents act primarily through their ability to induce DNA damage causing tumour growth inhibition. However, these agents cause cell cycle arrest by induction of checkpoints at either S-phase or G2-M boundary. The G2 arrest allows the cell time to repair the damaged DNA before entering mitosis. Chk1 and an unrelated serine/threonine kinase, Chk2, play a central role in arresting the cell cycle at the G2-M boundary (O'Connell et al *EMBO J* (1997) vol 16 p545-554). Chk1/2 induce this checkpoint by phosphorylating serine 216 of the CDC25 phosphatase, inhibiting the removal of two inactivating phosphates on cyclin dependent kinases (CDKs) (Zheng et al *Nature* (1998) vol 395 p507-510). Another overlapping pathway mediated by p53 also elicits cycle arrest in response to DNA-damage. However, p53 is mutationally inactivated in many cancers, resulting in a partial deficiency in their ability to initiate a DNA-repair response. If Chk1 activity is also inhibited in p53-negative cancers, all ability to arrest and repair DNA in response to DNA-damage is removed resulting in

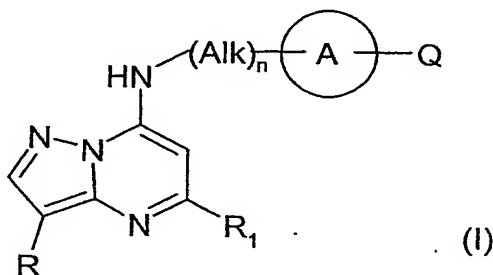
mitotic catastrophe and enhancing the effect of the DNA damaging agents (Konari et al Oncogene (2001) vol 20 p7453-7463; Bunch and Eastman Clin. Can. Res. (1996) vol 2 p791-797; Tenzer and Pruschy Curr. Med Chem (2003) vol 3 p35-46). In contrast, normal cells would be relatively unaffected due to retention of a competent p53-mediated cell-cycle arrest pathway. A Chk1 inhibitor (UCN-01) is now in phase I clinical trials for improving the efficacy of current DNA-damage inducing chemotherapeutic regimens (Sausville et al, J. Clinical Oncology (2001) vol19 p2319-2333).

#### Brief description of the invention

The present invention relates to the use of a class of amino pyrazolo[1,5-a]pyrimidine compounds as kinase inhibitors, for example CDK2 and/or PDK1 and/or CHK1 inhibitors, for example for inhibition of cancer cell proliferation. A core 7-amino pyrazolo[1,5-a]pyrimidine ring with aromatic substitution on the amino group are principle characterising features of the compounds with which the invention is concerned.

#### Detailed description of the invention

According to the present invention there is provided the use of a compound of formula (I) or a salt, N-oxide, hydrate or solvate thereof, in the preparation of a composition for inhibition of kinase activity:



wherein

Ring A is an optionally substituted carbocyclic or heterocyclic radical,

Alk represents an optionally substituted divalent C<sub>1</sub>-C<sub>6</sub> alkylene radical;

n is 0 or 1;

Q represents a radical of formula  $-(\text{Alk}^1)_p-(\text{X})_r-(\text{Alk}^2)_s-\text{Z}$  wherein in any compatible combination

Z is hydrogen or an optionally substituted carbocyclic or heterocyclic ring,

$\text{Alk}^1$  and  $\text{Alk}^2$  are optionally substituted divalent  $\text{C}_1\text{-C}_6$  alkylene radicals which may contain a  $-\text{O}-$ ,  $-\text{S}-$  or  $-\text{NR}^A-$  link, wherein  $\text{R}^A$  is hydrogen or  $\text{C}_1\text{-C}_6$  alkyl,

X represents  $-\text{O}-$ ,  $-\text{S}-$ ,  $-(\text{C}=\text{O})-$ ,  $-(\text{C}=\text{S})-$ ,  $-\text{SO}_2-$ ,  $-\text{SO}-$ ,  $-\text{C}(=\text{O})\text{O}-$ ,  $-\text{OC}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{NR}^A-$ ,  $-\text{NR}^A\text{C}(=\text{O})-$ ,  $-\text{C}(=\text{S})\text{NR}^A-$ ,  $-\text{NR}^A\text{C}(=\text{S})-$ ,  $-\text{SO}_2\text{NR}^A$ ,  $-\text{NR}^A\text{SO}_2-$ ,  $-\text{OC}(=\text{O})\text{NR}^A-$ ,  $-\text{NR}^A\text{C}(=\text{O})\text{O}-$ , or  $-\text{NR}^A-$  wherein  $\text{R}^A$  is hydrogen or  $\text{C}_1\text{-C}_6$  alkyl,

p, r and s are independently 0 or 1, and

$\text{R}_1$  represents a radical  $-(\text{Alk}^3)_a-(\text{Y})_b-(\text{Alk}^4)_d-\text{B}$  wherein a, b and d are independently 0 or 1,

$\text{Alk}^3$  and  $\text{Alk}^4$  are optionally substituted divalent  $\text{C}_1\text{-C}_3$  alkylene radicals,

Y represents a monocyclic divalent carbocyclic or heterocyclic radical having from 5 to 8 ring atoms,  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{NR}^A-$  wherein  $\text{R}^A$  is hydrogen or  $\text{C}_1\text{-C}_6$  alkyl,

B represents hydrogen or halo, or an optionally substituted monocyclic carbocyclic or heterocyclic ring having from 5 to 8 ring atoms, or in the case where Y is  $-\text{NR}^A-$  and b is 1, then  $\text{R}^A$  and the radical  $-(\text{Alk}^4)_d-\text{B}$  taken together with the nitrogen to which they are attached may form an optionally substituted heterocyclic ring,

R represents hydrogen, halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylthio, phenyl, benzyl, cycloalkyl with 3 to 6 ring atoms, or a monocyclic heterocyclic group having 5 or 6 ring atoms.

In particular, the invention relates to the use of such compounds in the preparation of a composition for inhibiting CDK2 and/or PDK1 and/or CHK1 activity.

As used herein, the term "(C<sub>a</sub>-C<sub>b</sub>)alkyl" wherein a and b are integers refers to a straight or branched chain alkyl radical having from a to b carbon atoms. Thus when a is 1 and b is 6, for example, the term includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein the term "divalent (C<sub>a</sub>-C<sub>b</sub>)alkylene radical" wherein a and b are integers means a saturated hydrocarbon chain having from a to b carbon atoms and two unsatisfied valences.

As used herein the unqualified term "cycloalkyl" refers to a saturated carbocyclic radical having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic radical, and to two such radicals covalently linked to each other, Illustrative of such radicals are phenyl, biphenyl and naphthyl.

As used herein the unqualified term "carbocyclic" refers to a cyclic radical whose ring atoms are all carbon and to two such cyclic radicals covalently linked to each other, and includes aryl, and cycloalkyl radicals. Typically, carbocyclic radicals will have from 3 to 14 ring atoms.

As used herein the term "heteroaryl" refers to a mono-, bi- or tri-cyclic aromatic radical containing one or more heteroatoms selected from S, N and O. Illustrative of such radicals are thienyl, benzthienyl, furyl, benzfuryl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, isothiazolyl,



benzothiazolyl, pyrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, triazolyl, benztriazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolyl and indazolyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in particular means a mono-, bi- or tri-cyclic non-aromatic radical containing one or more heteroatoms selected from S, N and O, and to groups consisting of a monocyclic non-aromatic radical containing one or more such heteroatoms which is covalently linked to another such radical or to a monocyclic carbocyclic radical. Typically, a heterocyclic radical will have from 5 to 14 ring atoms. Illustrative of such radicals are pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzfuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, maleimido and succinimido groups.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with at least one substituent, for example selected from (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, hydroxy, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, mercapto, mercapto(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, halo (including fluoro and chloro), trifluoromethyl, trifluoromethoxy, nitro, nitrile (-CN), oxo, phenyl, phenoxy, benzyl, benzyloxy, monocyclic carbocyclic or heterocyclic having from 5 to 7 ring atoms, -COOH, -COOR<sup>A</sup>, -COR<sup>A</sup>, -SO<sub>2</sub>R<sup>A</sup>, -CONH<sub>2</sub>, -SO<sub>2</sub>NH<sub>2</sub>, -CONHR<sup>A</sup>, -SO<sub>2</sub>NHR<sup>A</sup>, -CONR<sup>A</sup>R<sup>B</sup>, -SO<sub>2</sub>NR<sup>A</sup>R<sup>B</sup>, -NH<sub>2</sub>, -NHR<sup>A</sup>, -NR<sup>A</sup>R<sup>B</sup>, -OCONH<sub>2</sub>, -OCONHR<sup>A</sup>, -OCONR<sup>A</sup>R<sup>B</sup>, -NHCOR<sup>A</sup>, -NHCOOR<sup>A</sup>, -NR<sup>B</sup>COOR<sup>A</sup>, -NHCOOR<sup>A</sup>, -NR<sup>B</sup>COOR<sup>A</sup>, -NHCOOR<sup>A</sup>, -NR<sup>B</sup>COOR<sup>A</sup>, -NHCONH<sub>2</sub>, -NR<sup>A</sup>CONH<sub>2</sub>, -NHCONHR<sup>B</sup>, -NR<sup>A</sup>CONHR<sup>B</sup>, -NHCONR<sup>A</sup>R<sup>B</sup>, or -NR<sup>A</sup>CONR<sup>A</sup>R<sup>B</sup> wherein R<sup>A</sup> and R<sup>B</sup> are independently a (C<sub>1</sub>-C<sub>6</sub>)alkyl group or phenyl. The term "optional substituent" includes one of the foregoing substituent groups.

As used herein the term "salt" includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts,

including pharmaceutically or veterinarily acceptable salts, with bases such as alkali metal hydroxides, e.g. sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. N-ethyl piperidine, dibenzylamine and the like. Those compounds (I) which are basic can form salts, including pharmaceutically or veterinarily acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic and p-toluene sulphonic acids and the like.

Some compounds of the invention contain one or more actual or potential chiral centres because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereoisomers and mixtures thereof.

#### The ring A

Ring A is an optionally substituted carbocyclic or heterocyclic radical, preferably monocyclic aryl or heteroaryl radical. Examples of ring A include phenyl, naphthyl, 2-, 3- and 4-pyridyl, 5-pyrimidinyl, 2- and 3-thienyl, 2- and 3-furyl, piperazinyl, pyrrolidinyl, and thiazolynyl. Currently it is preferred that ring A is a phenyl ring.

Ring A may be optionally substituted by any of the substituents listed above in the definition of "optionally substituted". Examples of optional substituents on ring A or ring B include methyl, ethyl, methylenedioxy, ethylenedioxy, methoxy, ethoxy, methylthio, ethylthio, hydroxy, hydroxymethyl, hydroxyethyl, mercapto, mercaptomethyl, mercaptoethyl, amino, mono- and di-methylamino, mono- and di-ethylamino, fluoro, chloro, bromo, cyano, N-morpholino, N-piperidinyl, N-piperazinyl (the latter being optionally C<sub>1</sub>-C<sub>6</sub> alkyl- or benzyl-substituted on the free ring nitrogen), dimethylaminosulfonyl, phenylsulfonyl or phenoxy.

### The radical $-(\text{Alk})_n-$

When present, the Alk radical acts as a spacer radical between the amino group on the pyrazolo[1,5-a]pyrimidine ring and the ring A, and may be, for example  $-\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}(\text{CH}_3)-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$ ,  $-\text{CH}_2\text{CH}=\text{CH}-$ ,  $-\text{CH}_2\text{CH}=\text{CHCH}_2-$ ,  $-\text{CH}=\text{CHCH}=\text{CH}-$ ,  $-\text{C}\equiv\text{C}-$ ,  $-\text{CH}_2\text{C}\equiv\text{C}-$ , or  $-\text{CH}_2\text{C}\equiv\text{CCH}_2-$ . Presently it is preferred that Alk, when present, is  $-\text{CH}_2-$  or  $-\text{CH}_2\text{CH}_2-$ .

However, in another preferred class of compounds with which the invention is concerned, n may be 0 so that the ring A is directly linked to the amino group on the pyrazolo[1,5-a]pyrimidine ring.

### The Q Substituent

In the simplest structures with which the invention is concerned, each of p, r and s may be 0, and Z may be hydrogen, so that ring A is simply a carbocyclic or heterocyclic radical, preferably monocyclic aryl or heteroaryl radical, optionally substituted as discussed above. Substituents which are presently preferred, when ring A is optionally substituted phenyl, are dimethylaminosulfonyl, phenylsulfonyl or phenoxy especially in the 4-position.

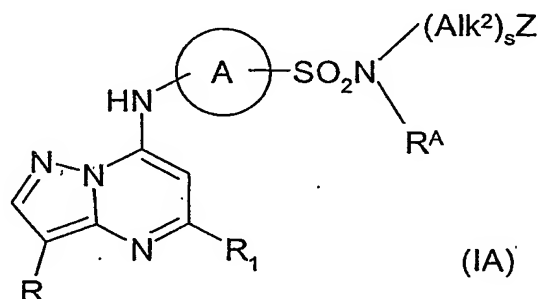
In other simple structures, p, r and s may again each be 0, and Z may be an optionally substituted carbocyclic or heterocyclic ring, for example phenyl, cyclopentyl, cyclohexyl, pyridyl, morpholino, piperidinyl, or piperazyl ring. In such cases, Z is a direct substituent in the optionally substituted ring A.

In more complex structures with which the invention is concerned, one or more of p, r and s may be 1, and Z may be hydrogen or an optionally substituted carbocyclic or heterocyclic ring. For example, p and/or s may be 1 and r may be 0, so that Z is linked to ring A by an alkylene radical, for example a  $\text{C}_1$ - $\text{C}_3$  alkylene radical, which is optionally substituted. In other cases each of p, r, and s may be 1, in which cases, Z is linked to ring A by an alkylene radical which is interrupted by the hetero atom-containing X radical. In still other cases, p and s may be 0 and r may be 1, in which case Z is linked

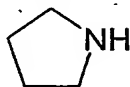
to ring A via the hetero atom-containing X radical. In a preferred example of the latter case, ring A is phenyl, p and s are each 0, X is  $-\text{SO}_2-$  or  $-\text{O}-$  on the 4-position of the phenyl ring A, and Z is phenyl (optionally substituted).

In other preferred embodiments, p is 0, r is 1, and X is a sulfonamide radical  $-\text{NR}^{\text{A}}\text{SO}_2-$  or a carboxamide radical  $-\text{NR}^{\text{A}}\text{C}(=\text{O})-$  ( $\text{R}^{\text{A}}$  being as defined above, but preferably hydrogen), with the N atom linked to the ring A. In such cases s may be 1 and Z may be hydrogen, so that the group Q is an alkylsulfonamido or carboxamido substituent in the ring A; or s may be 0 and Q may be an optionally substituted carbocyclic or heterocyclic ring such as optionally substituted phenyl, eg 4-methylphenyl, so that the group Q is an optionally substituted phenylsulfonamido or carboxamido substituent in the ring A.

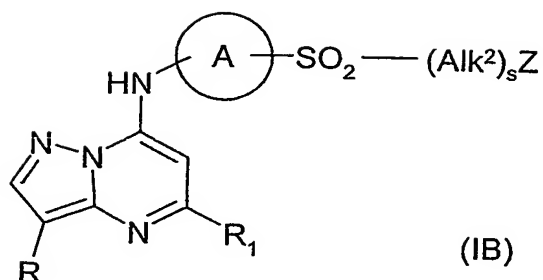
In another preferred subclass of compounds of the invention, p is 0, r is 1, and X is a sulfonamide radical  $-\text{NR}^{\text{A}}\text{SO}_2-$  ( $\text{R}^{\text{A}}$  being as defined above), with the S atom linked to the ring, ie a compound of structure (IA):



In compounds of structure (IA)  $\text{R}^{\text{A}}$  may be, for example methyl or phenyl, and  $-\text{Alk}^2)_s\text{Z}$  may be, for example methyl or hydrogen; or  $\text{R}^{\text{A}}$  and  $-\text{Alk}^2)_s\text{Z}$ , taken together with the nitrogen to which they are attached may form a ring such as:



In a further preferred subclass of compounds of the invention, p is 0, r is 1, and X is a sulfonyl radical  $-\text{SO}_2-$  ie a compound of structure (IB):



### The substituent $R_1$

$R_1$  represents a radical  $-(Alk^3)_a-(Y)_b-(Alk^4)_d-B$  as defined above.

In one class of compounds of the invention  $a$ ,  $b$  and  $d$  are all 0, and  $B$  is hydrogen or halo, so that the pyrimidine ring is either unsubstituted or substituted by halogen, for example chloro or bromo.

In another class of compounds of the invention,  $B$  is an optionally substituted monocyclic carbocyclic or heterocyclic ring, for example cyclopentyl, cyclohexyl, phenyl, 2-,3-, or 4-pyridyl, 2-, or 3-thienyl, 2-, or 3-furanyl, pyrrolyl, pyranlyl, or piperidinyl ring. Of the foregoing, cyclohexyl, and piperidin-1-yl are presently preferred. Optional substituents in ring  $B$  may be any of the substituents listed above in the definition of "optionally substituted". Examples of optional substituents on ring  $B$  include methyl, ethyl, methoxy, ethoxy, methylenedioxy, ethylenedioxy, methylthio, ethylthio, hydroxy, hydroxymethyl, hydroxyethyl, mercapto, mercaptomethyl, mercaptoethyl, amino, mono- and di-methylamino, mono- and di-ethylamino, fluoro, chloro, bromo, cyano, N-morpholino, N-piperidinyl, N-piperazinyl (the latter being optionally  $C_1$ - $C_6$  alkyl- or benzyl-substituted on the free ring nitrogen). Of the foregoing substituents, amino, is currently preferred, particularly when in the 4- position of a cyclohexyl or piperidin-1-yl ring  $B$ . In such cases, ring  $B$  is linked to the pyrimidine ring via linker radical of various types depending on the values of  $a$ ,  $b$  and  $d$ , and the identities of  $Alk^3$ ,  $Y$  and  $Alk^4$ . For example, when  $b$  is 0, the ring  $B$  is linked to the pyrimidine ring via an optionally substituted  $C_1$ - $C_6$  alkylene radical, methylene being presently preferred; and when  $a$  and  $d$  are 0 and  $b$  is 1 the ring  $B$  is linked to the pyrimidine ring via an oxygen or sulfur link or via an amino link  $-NR^A$ - wherein  $R^A$  is hydrogen or  $C_1$ - $C_6$  alkyl such as

methyl or ethyl. In the latter case, ie where a and d are each 0 and b is 1, it is presently preferred that Y is  $-O-$  or  $-NH-$ ,

In another class of compounds of the invention b is 0, at least one of a and d is 1, and B is hydrogen, so that the pyrimidine ring is substituted by a  $C_1-C_6$  alkyl group, for example methyl, ethyl, and n- or iso-propyl, which may itself be substituted by substituents listed above in the definition of "optionally substituted". Examples of optional substituents include methoxy, ethoxy, methylthio, ethylthio, hydroxy, hydroxymethyl, hydroxyethyl, mercapto, mercaptomethyl, mercaptoethyl, amino, mono- and di-methylamino, mono- and di-ethylamino, fluoro, chloro, bromo, and cyano.

In a further class of compounds of the invention a is 1 or 0, b is 1, Y is  $-NR^A-$ , and the radical  $-(Alk^4)_d-B$  taken together with  $R_A$  and the nitrogen to which they are attached form an optionally substituted heterocyclic ring such as a ring piperidiny, morpholinyl or piperazinyl ring, optionally substituted, for example, by hydroxy, mercapto, methoxy, ethoxy, methylthio, ethylthio, amino, mono- or dimethyl amino, mono- or diethyl amino, nitro, or cyano. In the case of a piperazinyl ring, the second ring nitrogen may optionally be substituted by, for example methyl or ethyl.

Specific examples of  $R_1$  include those present in the compounds of the Examples herein, especially cyclohexyloxy; cyclohexylamino; cyclohexylmethyl, and piperidin-1-ylmethyl, all optionally substituted in the ring by amino, particularly in the 4-position, for example by amino, or hydroxy.

#### The group R

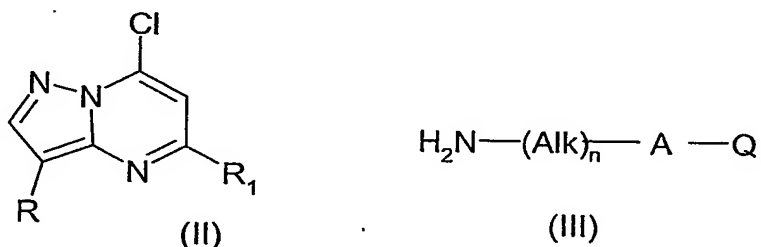
R may be, for example, hydrogen, chloro, bromo methyl, ethyl, n-propyl, iso-propyl, n-, sec- or tert-butyl, methoxy, methylthio, ethoxy, ethylthio, phenyl, benzyl, cyclopropyl, cyclopentyl, cyclohexyl, 2-, 3-, or 4- pyridyl, phenyl, pyridyl, morpholino, piperidiny, or piperazyl ring. At present it is preferred that R be chloro, bromo, cyclopentyl, cyclopropyl or isopropyl.

Specific compounds with which the invention is concerned include those identified in the Examples.

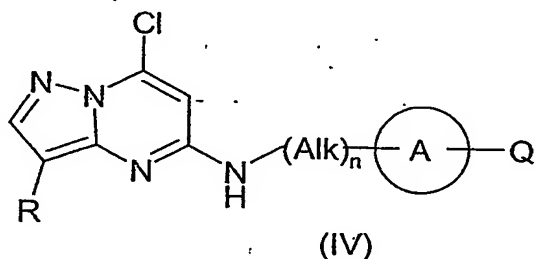
Novel compounds of formula (I) as discussed also form an aspect of the invention, particularly those wherein n is 0, ring A is optionally substituted phenyl (for example 3-chlorophenyl or 3-methoxyphenyl), Q is dimethylaminosulfonyl, phenylsulfonyl or phenoxy, R<sup>1</sup> is 4-aminocyclohexyloxy; 4-aminocyclohexylamino; 4-hydroxycyclohexylamino, 4-aminocyclohexylmethyl, or 4-aminopiperidin-1-ylmethyl, and R is chloro, bromo, cyclopentyl, cyclopropyl or isopropyl.

Compounds with which the invention is concerned may be prepared by literature methods, such as those of the preparative Examples herein, and methods analogous thereto.

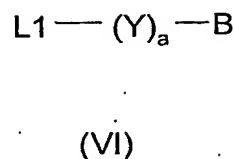
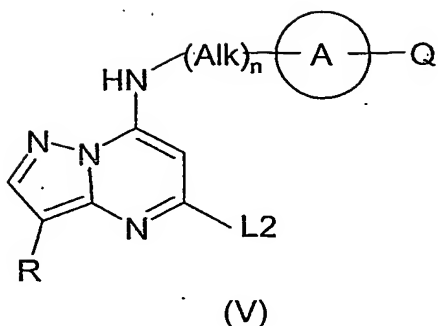
For example, compounds of the invention wherein R<sub>1</sub> is hydrogen or halo may be prepared by reacting the chloro or dichloro compound (II) with the amine (III),



and in the case where R<sub>1</sub> is halo, separating the desired compound (I) from any resultant contaminant regioisomer (IV):

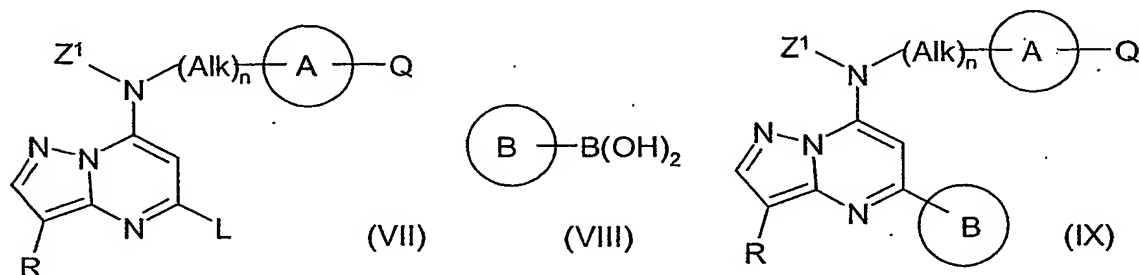


To prepared compounds of the invention wherein R<sub>1</sub> is a radical  $-(Y)_a-B$  the general synthetic procedure is based on the coupling of compounds (V) and (VI)

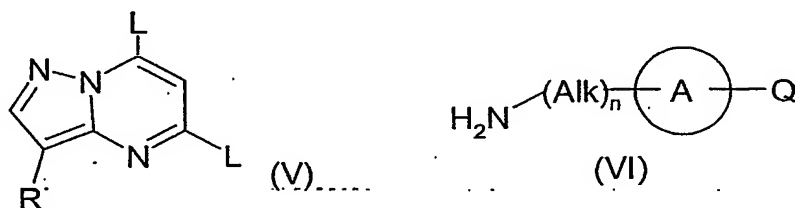


wherein L1 and L2 represent components of a leaving group L1L2.

Thus, to prepare compounds (I) wherein  $\text{R}_1$  is  $-(\text{Y})_a-\text{B}$  wherein  $a=0$  and B is an aryl or heteroaryl ring, a compound of formula (VII) wherein Z is an N-protecting group may be reacted with the corresponding aryl or heteroaryl borohydrate compound (VIII) to prepare an intermediate compound (IX), from which the N-protecting group  $\text{Z}^1$  may be removed to prepare the desired compound (I).



The starting compound (II) may be prepared by reaction of a compound (V) with an amine (VI):



In the above formulae (II) – (VI), L signifies a leaving group such as halo, for example chloro. Ring A, Alk, Q and n are as defined in relation to formula (I).



Likewise, to prepare compounds (I) wherein  $R_1$  is  $-(Y)_a-B$  wherein  $a=1$ , and  $Y$  is  $-O-$  the compound (VII), where  $L$  is chloro, for example, may be reacted with the hydroxy compound  $HY-B$ .

The compounds of the invention are inhibitors of kinases, for example CDK2 and/or PDK1 and/or CHK1, and are thus useful in the treatment of diseases which are mediated by excessive or inappropriate activity of such kinases, such as cancers, leukemias and other disease states associated with uncontrolled cell proliferation such as psoriasis and restenosis

Accordingly, the invention also provides:

- (i) a method of treatment of diseases or conditions mediated by excessive or inappropriate kinase activity, for example CDK2 and/or PDK1 and/or CHK1 activity in mammals, particularly humans, which method comprises administering to the mammal an amount of a compound of formula (I) as defined above, or a salt, hydrate or solvate thereof, effective to inhibit said kinase activity.; and
- (ii) a compound of formula (I) as defined above, or a salt hydrate or solvate thereof, for use in human or veterinary medicine, particularly in the treatment of diseases or conditions mediated by excessive or inappropriate kinase activity, for example CDK2 and/or PDK1 and/or CHK1 activity;

It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the causative mechanism and severity of the particular disease undergoing therapy. In general, a suitable dose for orally administrable formulations will usually be in the range of 0.1 to 3000 mg once, twice or three times per day, or the equivalent daily amount administered by infusion or other routes. However, optimum dose levels and frequency of dosing will be determined by clinical trials as is conventional in the art.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. The orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceuticals such as the British Pharmacopoeia.

The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants

such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

The following non-limiting Examples illustrate the invention:

In the Examples, reactions that are specified as being carried out in a microwave oven were conducted in a Smith Synthesizer. Proton NMR experiments were conducted on a Bruker DPX400 ultra shield NMR spectrometer in the solvent specified.

#### LC-MS: Method A

HPLC: HP1100  
 Column: Luna 3 $\mu$ m, C18(2), 30mm x 4.6mm i.d. from Phenomenex  
 Temperature: 22°C  
 Solvents: A - Water + 10mmol ammonium acetate + 0.08% (v/v) formic acid  
 B - 95% Acetonitrile / 5% Solvent A + 0.08% (v/v) formic acid  
 Flow rate: 2ml/min

Time (mins)	% Solvent A	% Solvent B	Flow (ml/min)
0	95	5	2
0.25	95	5	2
2.50	5	95	2
2.55	5	95	3
3.60	5	95	3
3.65	5	95	3
3.70	5	95	2
3.75	95	5	2

Gradient

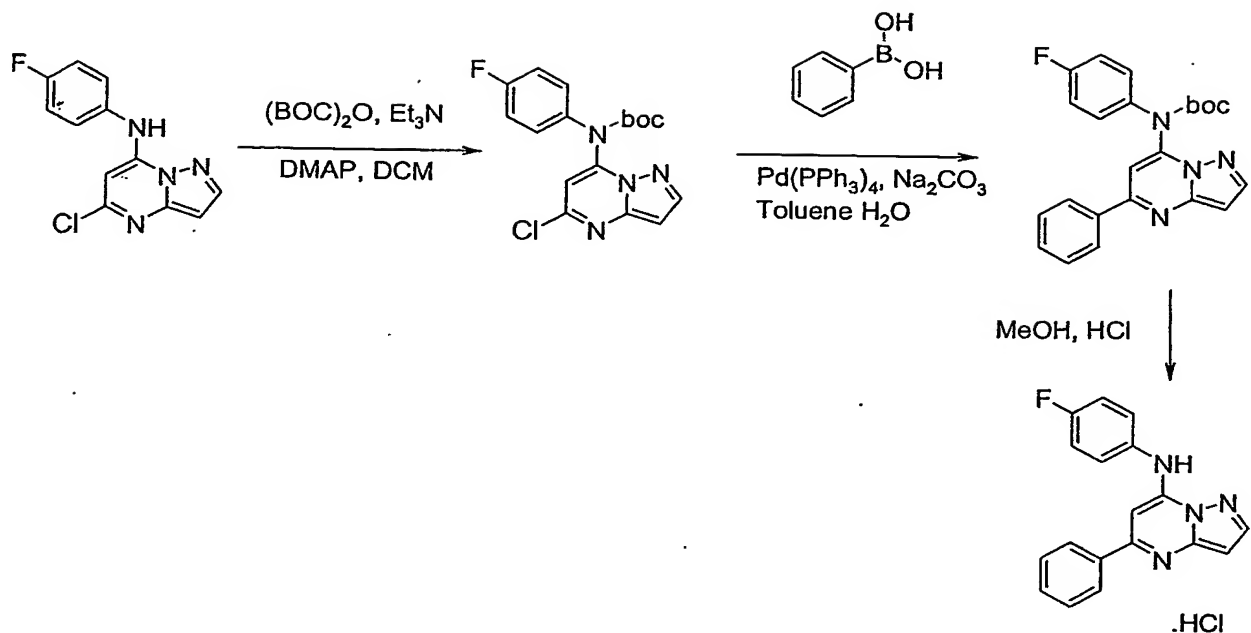
Total acquisition time is 3.75minutes

Detection: UV detection at 230nm, 254nm and 270nm

Mass Spec: HP1100 MSD, Series A

Ionisation is positive or negative ion electrospray

Molecular weight scan range is 120-1000

**Example 1****Step 1****5-Chloro-7-(4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine**

To a solution of 5,7-dichloropyrazolo[1,5-a]pyrimidine<sup>1</sup> (0.35 g, 1.86 mmol) in ethanol ( $15 \text{ cm}^3$ ) was added 4-fluoroaniline ( $0.35 \text{ cm}^3$ , 3.72 mmol). The reaction mixture was heated under reflux for 1 hour. The reaction mixture was concentrated *in vacuo* and the product purified on silica eluting with 15% ethyl acetate in hexanes, to yield the title compound as a white solid (0.42 g, 86%).

$\delta_{\text{H}}$  (400 MHz;  $\text{d}_4\text{-MeOH}$ ) 8.02 (1 H, d,  $J$  2.2 Hz), 7.40-7.36 (2 H, m), 7.21 (2H, t,  $J$  6.7), 6.32 (1 H, d,  $J$  2.2 Hz), 5.97 (1H, s).

$m/z$  263 and 265 (each  $M+H$ , 100% and 30%) retention time 2.54 min (Method A).

**Step 2****5-Chloro-7-(N-tert-butoxycarbonyl-4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine**

To a solution of 5-chloro-7-(4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine (0.15 g, 0.57 mmol) in dichloromethane (10 cm<sup>3</sup>) was added di-*tert*-butyl dicarbonate (0.37 g, 1.71 mmol), triethylamine (0.096 cm<sup>3</sup>, 0.69 mmol) and 4-dimethylaminopyridine (0.01 g, 0.082 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction was diluted with water (30 cm<sup>3</sup>) and extracted with dichloromethane (3 × 20 cm<sup>3</sup>). The combined organic fractions were washed with brine then dried with magnesium sulphate and concentrated *in vacuo*. The product was purified on silica eluting with 20% ethyl acetate in hexanes, to yield the title compound as a white solid (0.191 g, 92%).

$\delta_{\text{H}}$  (400 MHz; d-CHCl<sub>3</sub>) 8.09 (1 H, d, *J* 2.3 Hz), 7.29-7.25 (2 H, m), 6.99 (2H, t, *J* 8.1), 6.63 (1 H, d, *J* 2.3 Hz), 6.60 (1H, s), 1.30 (9H, s).

### Step 3

#### 5-Phenyl-7-(*N*-tert-butoxycarbonyl-4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine

To a solution of 5-chloro-7-(*N*-tert-butoxycarbonyl-4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine (0.05 g, 0.14 mmol) in toluene (3.5 cm<sup>3</sup>) and water (1 cm<sup>3</sup>) was added phenyl boronic acid (0.02 g, 0.16 mmol) and sodium carbonate (0.031 g, 0.29 mmol). The solution was degassed by bubbling nitrogen through the reaction mixture for 5 min. Tetrakis(triphenylphosphine)palladium(0) (0.015 g, 0.012 mmol) was added to the mixture and the reaction was heated at reflux for 16 h. The reaction mixture was concentrated *in vacuo* and purified on silica eluting with 20% ethyl acetate in hexanes to yield the title compound as an off-white solid (0.048 g, 86%).

$\delta_{\text{H}}$  (400 MHz; d-CHCl<sub>3</sub>) 8.11 (1 H, d, *J* 2.3 Hz), 7.99-7.97 (2 H, m), 7.44-7.42 (3H, m), 7.34-7.31 (2 H, m), 7.08 (1H, s), 6.97 (2H, t, *J* 8.3 Hz), 6.73 (1H, d, *J* 2.3 Hz), 1.31 (9H, s).

*m/z* 405 (*M*+*H*, 80%), 349 (*M*+*H*- 56, 70%), 305 (*M*+*H*- 100, 100%), retention time 2.92 min (Method A).

#### Step 4

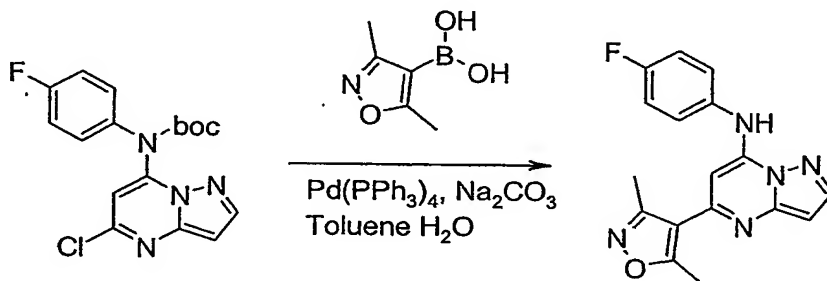
#### 5-Phenyl-7-(4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine hydrochloride

To a solution of 5-phenyl-7-(*N*-tert-butoxycarbonyl-4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine (0.045 g, 0.11 mmol) in methanol (1 cm<sup>3</sup>) was added a solution of hydrochloric acid (3 M in methanol, 10 cm<sup>3</sup>). The reaction mixture was stirred at room temperature for 3 h then concentrated *in vacuo*. The product was purified by crystallisation from ethyl acetate, to yield the title compound as a white solid (0.016 g, 42%).

$\delta_{\text{H}}$  (400 MHz; d<sub>4</sub>-MeOH) 8.25 (1 H, d, *J* 2.2 Hz), 7.74-7.72 (2 H, m), 7.59-7.51 (5H, m), 7.27 (2H, t, *J* 8.6 Hz), 6.60 (1H, d, *J* 2.2 Hz), 6.39 (1H, s).

*m/z* 305 (*M*+H, 100%), retention time 2.68 min (Method A).

#### Example 2



#### 5-(3,5-Dimethylisoxazole)-7-(4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine

To a solution of 5-chloro-7-(*N*-tert-butoxycarbonyl-4-fluorophenylamino)pyrazolo[1,5-a]pyrimidine (Example 1, Step 2) (0.05 g, 0.14 mmol) in 1,4-dioxane (3.5 cm<sup>3</sup>) and water (1 cm<sup>3</sup>) was added 3,5-dimethylisoxazole-4-boronic acid (0.023 g, 0.16 mmol) and sodium carbonate (0.031 g, 0.29 mmol). The solution was degassed by bubbling nitrogen through the mixture for 5 min. Tetrakis(triphenylphosphine)palladium(0) (0.015 g, 0.012 mmol) was added to the mixture and the reaction heated at 150°C for

10 min in a microwave oven. The reaction mixture was concentrated *in vacuo* and purified on silica eluting with 2% methanol in dichloromethane to yield the title compound as a white solid (0.021 g, 47%).

$\delta_{\text{H}}$  (400 MHz;  $\text{d-CHCl}_3$ ) 8.03 (1 H, d,  $J$  2.3 Hz), 7.97 (1 H, s), 7.33-7.30 (2H, m), 7.13 (2H, t,  $J$  8.5 Hz), 6.52 (1H, d,  $J$  2.3 Hz), 6.13 (1H, s), 2.50 (3H, s), 2.34 (3H, s).

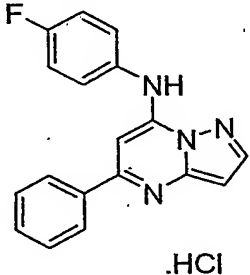
$m/z$  324 ( $M+H$ , 100%), retention time 2.51 min (Method A).

1. T. Novinson et al., Journal of Medicinal Chemistry (1976), 19(4), 512-16.

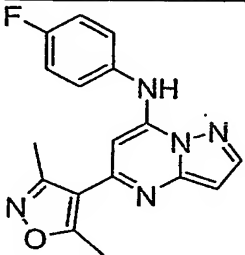
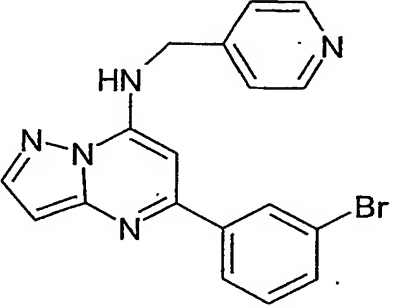
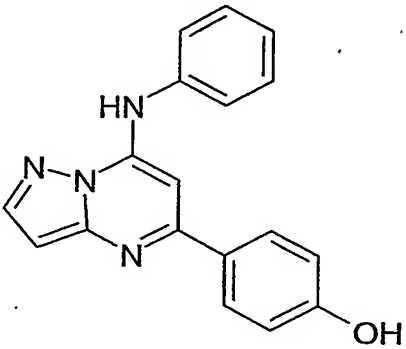
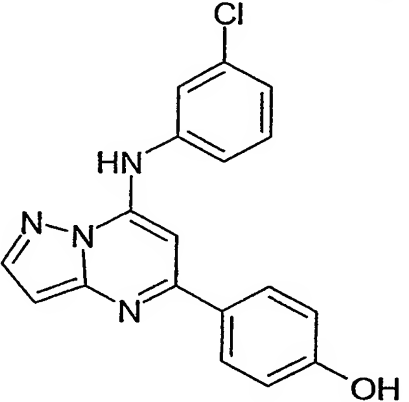
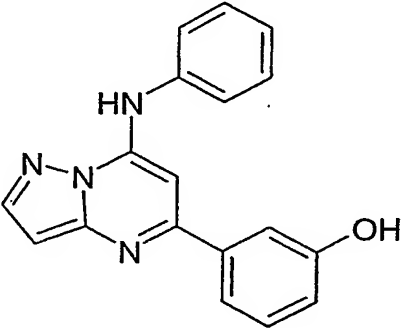
### Examples 3 – 8

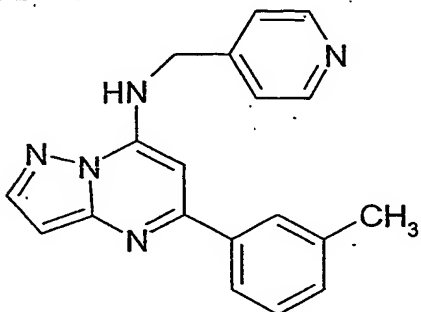
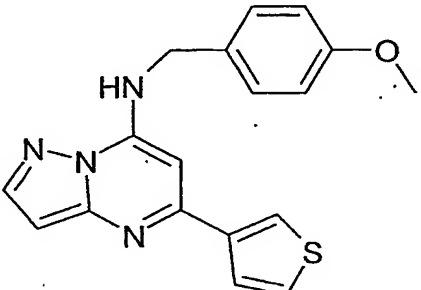
The compounds of Examples 3 – 8, listed in the following Table 1 were commercially available from BioFocus (BioFocus plc, Chesterford Park, Saffron Walden, Essex, CB10 1XL). The compounds of Examples 1 and 2 are also included in the Table. All compounds were tested for CDK2, CHK1 and PDK1 inhibitory activity in the assays described below in the Assay section. The result obtained in each case is given in the Table.

Table 1

Structure	Example	CDK2 IC <sub>50</sub> ( $\mu\text{M}$ )	Chk1 IC <sub>50</sub> ( $\mu\text{M}$ )	PDK1 IC <sub>50</sub> ( $\mu\text{M}$ )	$m/z$	RT (min)
	1	6.09	>200	>200	305 ( $M+H$ , 100%)	2.68

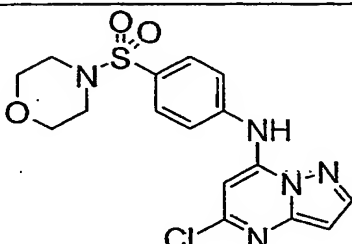


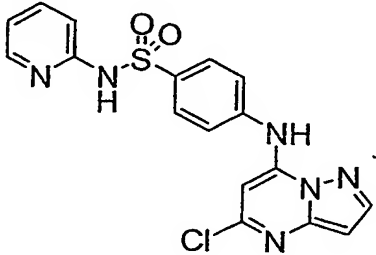
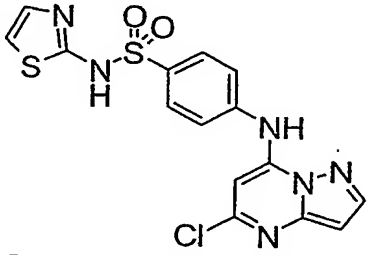
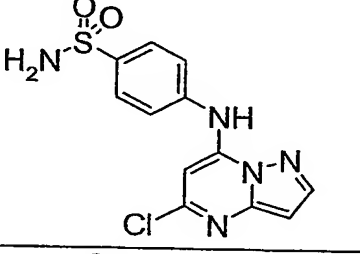
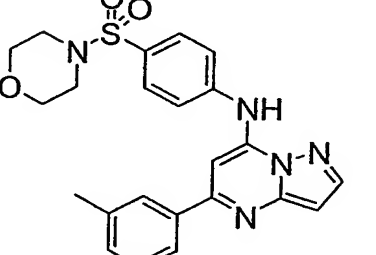
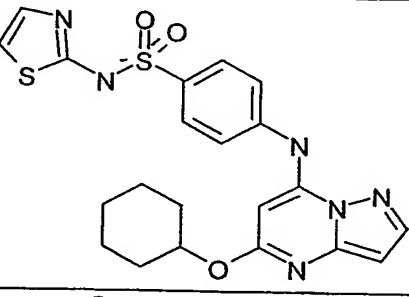
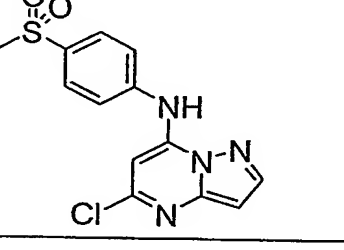
	2	13.37	>200	>200	324 ( <i>M</i> + <i>H</i> , 100%)	2.51
	3	1.64	29.6	34.6	380 and 382 (each <i>M</i> + <i>H</i> , 100%)	2.34
	4	3.76	>200	>200	303 ( <i>M</i> + <i>H</i> , 100%)	2.20
	5	3.96	>200	>200	337 ( <i>M</i> + <i>H</i> , 100%)	2.42
	6	5.65	>200	>200	303 ( <i>M</i> + <i>H</i> , 100%)	2.32

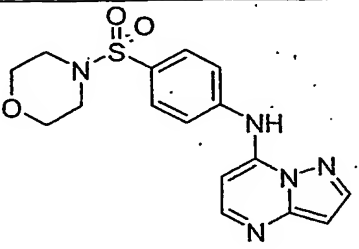
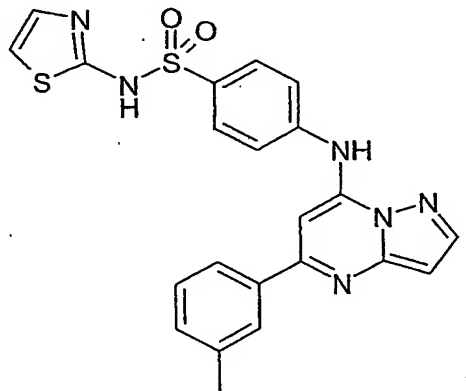
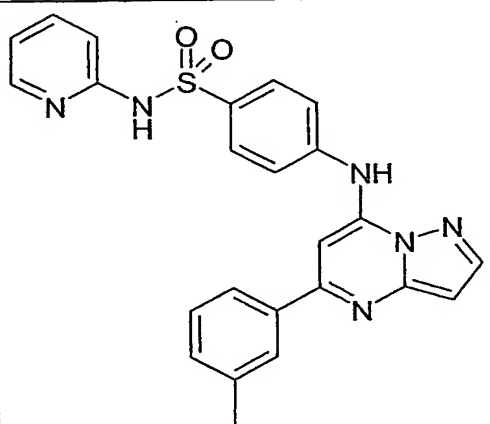
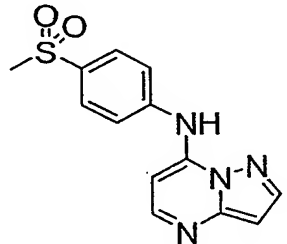
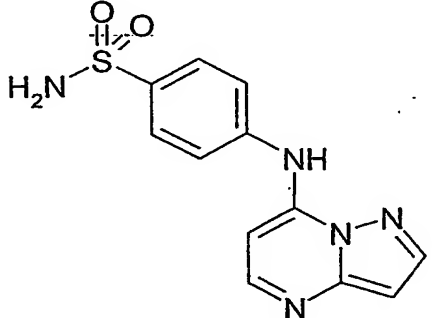
	7	7.19	>200	>200	316 (M+H, 100%)	2.07
	8	7.55	>200	>200	337 (M+H, 100%)	2.48

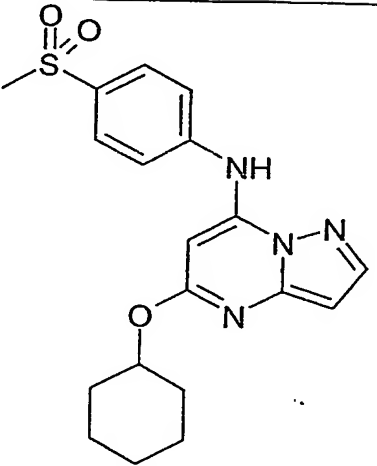
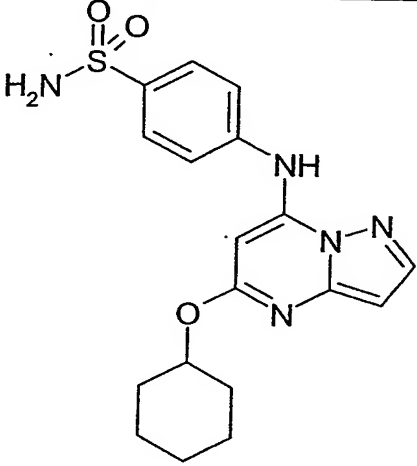
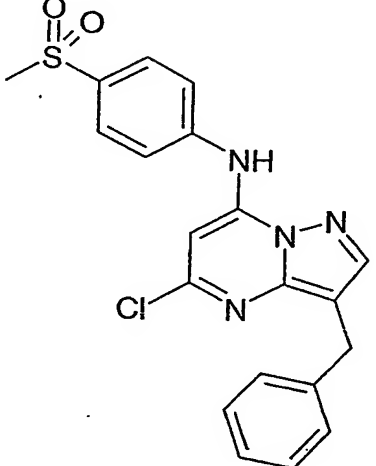
The compounds of Examples 9 – 23, listed in the following Table 2 were prepared by methods analogous to those of Example 1. All compounds were tested for CDK2, CHK1 and PDK1 inhibitory activity in the assays described below in the Assay section. The result obtained in each case is given in the Table.

Table 2

Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	m/z	RT (min)
	9	0.99	>200	>200	394 and 396 (each M+H, 100 and 35%)	2.33

	10	1.63	>200	>200	401 and 403 (each M+H, 100 and 35%)	2.05
	11	1.31	>200	>200	407 and 409 (each M+H, 100 and 35%)	2.10
	12	0.72	>200	>200	324 and 326 (each M+H, 100 and 35%)	2.02
	13	1.76	>200	>200	450 (M+H, 100%)	2.66
	14	0.59	>200	24.6	471 (M+H, 100%)	2.63
	15	1.99	>200	>200	323 and 325 (each M+H, 100 and 35%)	2.14

	16	3.35	>200	>200	360 (M+H, 100%)	1.98
	17	3.17	>200	31.6	463 (M+H, 100%)	2.36
	18	0.96	52.4	>200	457 (M+H, 100%)	2.36
	19	10.44	ND	>200	289 (M+H, 100%)	1.75
	20	1.76	>200	>200	290 (M+H, 100%)	1.59

	21	1.32	>200	>200	387 ( <i>M</i> + <i>H</i> , 100%)	2.73
	22	0.30	>200	70.3	388 ( <i>M</i> + <i>H</i> , 100%)	2.61
	23	>200	>200	>200	413 and 415 (each <i>M</i> + <i>H</i> , 100 and 35%)	2.86

Examples 24 and 25



To a solution of diisopropyl amine (25.2 cm<sup>3</sup>, 0.180 mol) in tetrahydrofuran (100 cm<sup>3</sup>) at -78°C was added dropwise n-butyllithium (1.6 M in hexanes, 112.8 cm<sup>3</sup>, 0.180 mol). The reaction was stirred at -78°C for 30 min. Isovaleronitrile (18.9 cm<sup>3</sup>, 0.180 mol) was added and the reaction stirred for 10 min. The reaction mixture was added to a solution of ethyl formate (15.3 cm<sup>3</sup>, 0.190 mol) in tetrahydrofuran (50 cm<sup>3</sup>) at -78°C. The reaction was stirred at -78°C for 30 min. then allowed to warm to room temperature and stirred for 16 h. The reaction was diluted with aqueous hydrochloric acid (300 cm<sup>3</sup>, 1M) until the pH was approximately pH = 3. The product was extracted with ethyl acetate (3 × 100 cm<sup>3</sup>). The combined organic fractions were washed with brine then dried over magnesium sulphate and concentrated *in vacuo*. The product was purified on silica gel eluting with 50% diethyl ether in hexanes, to yield the title compound as a yellow oil (14.6 g, 73%).

←  $\delta_H$  (400 MHz;  $d\text{-CHCl}_3$ ) 9.51 (1 H, d,  $J$  1.1 Hz), 3.35 (1H, dd,  $J$  4.9, 1.0), 2.43-2.38 (1H, m), 1.12 (3H, d,  $J$  6.6), 1.05 (3H, d,  $J$  6.7).

### Step 2: 3-amino-4-isopropylpyrazole

To a solution of 2-formyl-3-methyl-butanenitrile (9.47 g, 85.2 mmol) in ethanol (250  $\text{cm}^3$ ) was added hydrazine hydrate (6.27  $\text{cm}^3$ , 110.8 mmol) and acetic acid (8.30  $\text{cm}^3$ , 144.8 mmol). The reaction was heated under reflux for 16 h. The reaction was concentrated *in vacuo* to approximately one third the original volume. The residue was diluted with aqueous sodium bicarbonate (100  $\text{cm}^3$ , saturated solution) and the product extracted with dichloromethane ( $3 \times 100 \text{ cm}^3$ ). The combined organic fractions were washed with brine then dried over magnesium sulphate and concentrated *in vacuo* to yield the crude product as a brown solid (9.35 g, 88%).

$\delta_H$  (400 MHz;  $d\text{-CHCl}_3$ ) 6.99 (1 H, s), 2.55 (1H, sept,  $J$  6.8), 1.06 (6H, d,  $J$  6.8).

$m/z$  126 ( $M+H$ , 100%), retention time 1.21 min (Method A).

### Step 3: 3-isopropyl-5,7-dihydroxypyrazolo[1,5-a]pyrimidine

Sodium (0.98 g, 42.8 mmol) was dissolved in ethanol (200  $\text{cm}^3$ ) and to the solution was added 3-amino-4-isopropyl-pyrazole (4.46 g, 35.6 mmol) and diethyl malonate (5.95  $\text{cm}^3$ , 39.2 mmol). The reaction was heated under reflux for 16 h. The reaction was concentrated *in vacuo* and the residue dissolved in water (50  $\text{cm}^3$ ). The reaction was acidified to approx pH = 3 with hydrochloric acid (2N) and the precipitate formed was collected by filtration. The solid was washed with water ( $3 \times 50 \text{ cm}^3$ ) and dried *in vacuo* to yield the product as an off-white solid (3.95 g, 57%).

$\delta_H$  (400 MHz;  $d_6\text{-DMSO}$ ) 7.94 (1 H, s), 7.84 (1H, s), 5.06 (1H, s), 3.91 (2H, s), 3.23-3.08 (2H, m), 1.32 (6H, d,  $J$  6.8), 1.30 (6H, d,  $J$  6.8).

$m/z$  194 ( $M+H$ , 100%), retention time 1.38 min (Method A).

#### Step 4: 3-isopropyl-5,7-dichloropyrazolo[1,5-a]pyrimidine

3-isopropyl-5,7-dihydroxypyrazolo[1,5-a]pyrimidine (3.95 g, 20.4 mmol) and *N,N*-dimethylaniline (1.73 cm<sup>3</sup>, 13.6 mmol) were suspended in phosphorous oxychloride (38.1 cm<sup>3</sup>, 0.41 mol). The reaction was heated under reflux for 16 h, over which time the 3-isopropyl-5,7-dihydroxypyrazolo[1,5-a]pyrimidine dissolved. The reaction was concentrated *in vacuo* and the residue poured onto ice (approx 50 g). The product was extracted with dichloromethane (3 × 50 cm<sup>3</sup>). The combined organic fractions were washed with brine then dried over magnesium sulphate and concentrated *in vacuo*. The product was purified on silica eluting with 5% ethyl acetate in hexanes, to yield the title compound as a yellow solid (3.90 g, 83%).

$\delta_H$  (400 MHz; d-CHCl<sub>3</sub>) 7.92 (1 H, s), 6.74 (1H, s), 3.14 (1H, sept, *J* 6.9), 1.19 (6H, d, *J* 6.9).

*m/z* 230 and 232 each (*M*+H, 100% and 65%), retention time 2.65 min (Method A).

#### Step 5: 3-isopropyl-5-chloro-7-(4-methylsulphonylamino-phenyl)pyrazolo[1,5-a]pyrimidine (Example 24)

To a solution of 3-isopropyl-5,7-dichloropyrazolo[1,5-a]pyrimidine (0.50 g, 2.17 mmol) in ethanol (20 cm<sup>3</sup>) was added 4-methylsulphonylaniline (0.50 g, 2.39 mmol). The reaction was heated under reflux for 16 h. The reaction was concentrated *in vacuo* and the residue triturated with hot methanol (2 × 10 cm<sup>3</sup>) to yield the product as a white solid (0.56 g, 70%).

$\delta_H$  (400 MHz; d<sub>6</sub>-DMSO) 10.53 (1H, s), 8.05 (1 H, s), 7.85 (2H, d, *J* 6.8), 7.60 (2H, d, *J* 6.8), 6.28 (1H, s), 3.11 (3H, s), 3.02 (1H, sept, *J* 6.9), 1.18 (6H, d, *J* 6.9).

*m/z* 365 and 367 each (*M*+H, 100% and 35%), retention time 2.57 min (Method A).



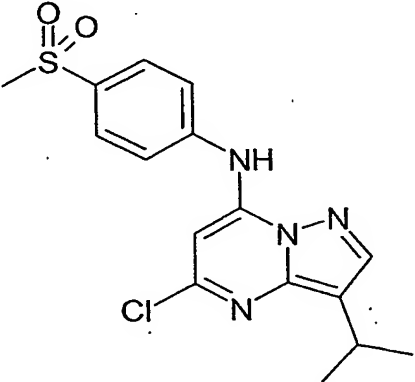
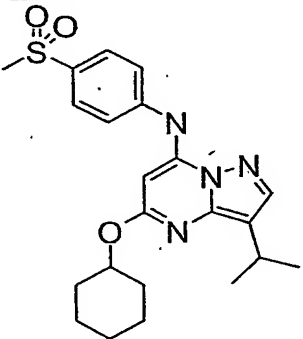
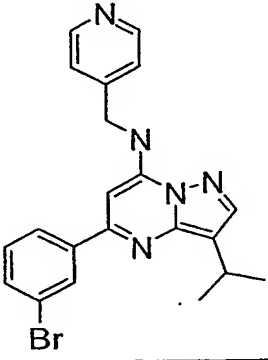
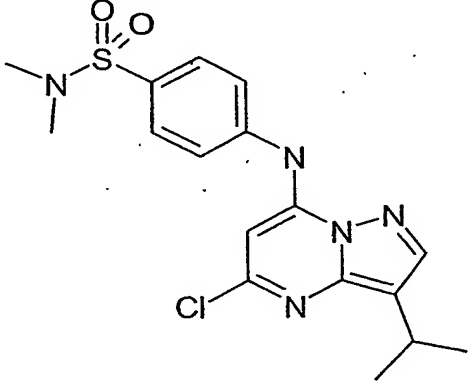
**Step 6: 3-isopropyl-5-cyclohexanyloxy-7-(4-methylsulphonylaminophenyl)pyrazolo[1,5-a]pyrimidine (Example 25)**

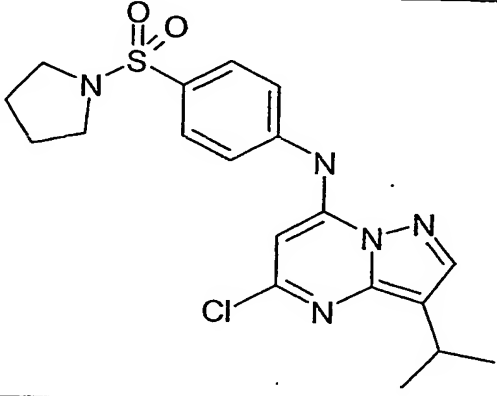
To a solution of cyclohexanol (0.14 cm<sup>3</sup>, 1.37 mmol) in dioxane (5 cm<sup>3</sup>) was added sodium hydride (0.11 g, 60% by wt in oil, 2.74 mmol). Once effervescence had ceased 3-isopropyl-5-chloro-7-(4-methylsulphonylaminophenyl)pyrazolo[1,5-a]pyrimidine (0.10 g, 0.27 mmol) was added. The reaction was heated via a microwave reactor, in a sealed tube, at 120 °C for 20 min. The reaction was poured into water (20 cm<sup>3</sup>) and the product extracted with ethyl acetate (3 × 20 cm<sup>3</sup>). The combined organic fractions were dried with brine then magnesium sulphate and concentrated *in vacuo*. The product was purified on silica eluting with 25-50% ethyl acetate in hexanes, to yield the title compound as a white solid (0.008 g, 7%).

$\delta_H$  (400 MHz; d-CDCl<sub>3</sub>) 8.18 (1 H, s), 7.98 (2H, d, *J* 6.8), 7.78 (1H, s), 7.48 (2H, d, *J* 6.8), 5.17-5.13 (1H, m), 3.15 (1H, sept, *J* 6.8), 3.07 (3H, s), 2.04-2.02 (2H, m), 1.80-1.77 (2H, m), 1.60-1.43 (6H, m), 1.35 (6H, d, *J* 6.9).  
*m/z* 429 (*M*+H, 100%), retention time 3.05 min (Method A).

The compounds of Examples 26 – 28, listed in the following Table 3 were prepared by methods analogous to those of Examples 24 and 25. The compounds of Examples 24 and 25 are also included in the Table. All compounds were tested for CDK2 inhibitory activity in the assay described below in the Assay section. The result obtained in each case is given in the Table 3.

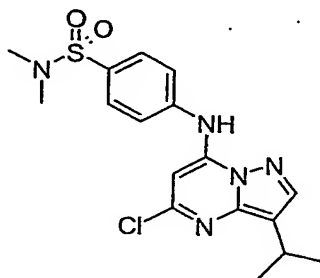
Table 3

Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	<i>m/z</i>	RT (min)
	24	0.22	365 and 367 (each <i>M</i> + <i>H</i> , 100 and 35%)	2.58
	25	0.95	429 ( <i>M</i> + <i>H</i> , 100 %)	3.05
	26	0.53	424 and 426 (each <i>M</i> + <i>H</i> , 100%)	2.67
	27	0.24	394 and 396 (each <i>M</i> + <i>H</i> , 100 and 35%)	2.81

	28	0.27	401 and 403 (each $M+H$ , 100 and 35%)	2.05
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**Example 29**

**3-isopropyl-5-chloro-7-(4-(*N,N*-dimethylsulphonamido)phenylamino)pyrazolo[1,5-*a*]pyrimidine**



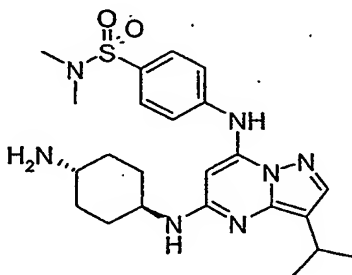
To a solution of 3-isopropyl-5,7-dichloropyrazolo[1,5-*a*]pyrimidine (0.15 g, 0.66 mmol) in ethanol (20 cm<sup>3</sup>) was added 4-amino-*N,N*-dimethylbenzenesulphonamide (0.146 g, 0.73 mmol). The reaction was heated at reflux for 16 h. The reaction was concentrated *in vacuo* and the residue triturated with hot ethanol (2 × 10 cm<sup>3</sup>) to yield the product as a white solid (0.23 g, 92%).

$\delta_H$  (400 MHz;  $d_6$ -DMSO) 10.41 (1H, s), 7.97 (1 H, s), 7.59 (2H, d,  $J$  6.7), 7.52 (2H, d,  $J$  6.7), 6.26 (1H, s), 2.94 (1H, sept,  $J$  6.9), 2.43 (6H, s), 1.10 (6H, d,  $J$  6.9).

$m/z$  394 and 396 each ( $M+H$ , 100% and 35%), retention time 2.78 min (Method A).

**Example 30**

**3-isopropyl-5-(*trans*-4-aminocyclohexylamino)-7-(4-(*N,N*-dimethylsulphonamido)phenylamino)pyrazolo[1,5-*a*]pyrimidine**



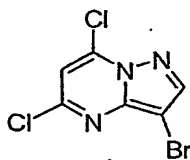
To a solution of 3-isopropyl-5-chloro-7-(4-(*N,N*-dimethylsulphonamido)phenylamino)pyrazolo[1,5-*a*]pyrimidine (0.40 g, 1.02 mmol) in dioxane (3 cm<sup>3</sup>) was added acetonitrile (1 cm<sup>3</sup>), 1,4-*trans*-diaminocyclohexane (1.17 g, 10.24 mmol) and triethylamine (0.71 cm<sup>3</sup>, 5.12 mmol). The reaction was heated via a microwave, in a sealed tube, at 180 °C for 2 hours. The reaction mixture was loaded onto a silica flash column and the product eluted with 15% methanol in dichloromethane, to yield the title compound as a white solid (0.088 g, 18%).

$\delta_{\text{H}}$  (400 MHz; d<sub>4</sub>-CDCl<sub>3</sub>) 8.00 (1 H, s), 7.74 (2H, d, *J* 6.7), 7.64 (1H, s), 7.36 (2H, d, *J* 6.7), 5.67 (1H, s), 4.41 (1H, d, *J* 7.8), 3.42-3.40 (1H, m), 3.05 (1H, sept, *J* 6.9), 2.89-2.81 (1H, m), 2.15 (2H, d, *J* 10.9), 1.93 (2H, d, *J* 9.2), 2.11-1.62 (2H, br s), 1.47-1.39 (2H, m), 1.27 (6H, d, *J* 6.9), 1.25-1.15 (2H, m). *m/z* 472 (*M*+H, 100%), retention time 1.93 min (Method A).

**Example 31**

**Step 1**

**3-bromo-5,7-chloropyrazolo[1,5-*a*]pyrimidine**



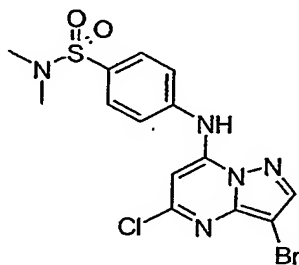
To a solution of 5,7-chloropyrazolo[1,5-*a*]pyrimidine (1 g, 5.32 mmol) in acetonitrile (20 cm<sup>3</sup>) was added *N*-bromosuccinimide (1.04 g, 5.85 mmol) and

ceric ammonium nitrate (0.029 g, 0.053 mmol). The reaction was heated at reflux for 1 hour. The reaction was washed with aqueous sodium metabisulfite (30 cm<sup>3</sup>, 10% solution) and then brine (20 cm<sup>3</sup>). The organic fraction was dried with magnesium sulphate and concentrated *in vacuo*. The product was purified on silica eluting with 20% ethylacetate in hexane, to yield the title compound as a yellow solid (1.33 g, 92%).

$\delta_H$  (400 MHz; d<sub>4</sub>-CDCl<sub>3</sub>) 8.22 (1H, s), 7.04 (1H, s).

## Step 2

**3-bromo-5-chloro-7-(4-(*N,N*-dimethylsulphonamido)phenylamino)pyrazolo[1,5-a]pyrimidine**



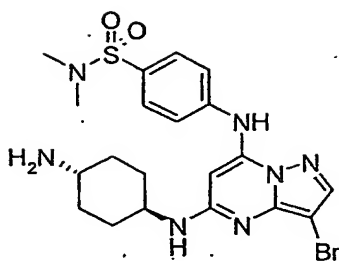
To a solution of 3-bromo-5,7-dichloropyrazolo[1,5-a]pyrimidine (0.14 g, 0.53 mmol) in ethanol (20 cm<sup>3</sup>) was added 4-amino-*N,N*-dimethbenzenesulphonamide (0.107 g, 0.53 mmol). The reaction was heated at reflux for 16 h. The reaction was concentrated *in vacuo* and the residue triturated with hot ethanol (2 × 10 cm<sup>3</sup>) to yield the product as a white solid (0.10 g, 43%).

$\delta_H$  (400 MHz; d<sub>4</sub>-CDCl<sub>3</sub>) 8.10 (1H, s), 7.89 (2H, d, *J* 6.7), 7.66 (2H, d, *J* 6.7), 6.51 (1H, s), 2.74 (6H, s).

*m/z* 430, 432 and 434 each (*M*+*H*, 75 %, 100% and 25%), retention time 2.58 min (Method A).

## Step 3

**3-bromo-5-(*trans*-4-aminocyclohexylamino)-7-(4-(*N,N*-dimethylsulphonamido)phenylamino)pyrazolo[1,5-a]pyrimidine**



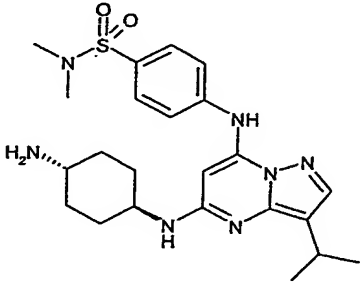
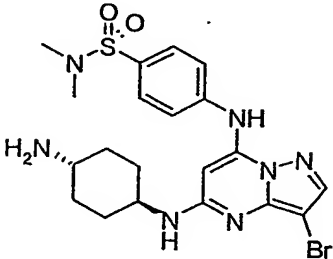
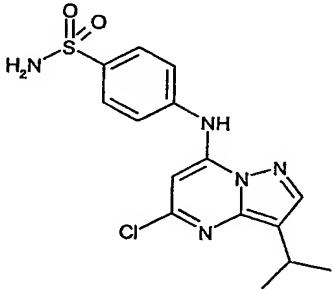
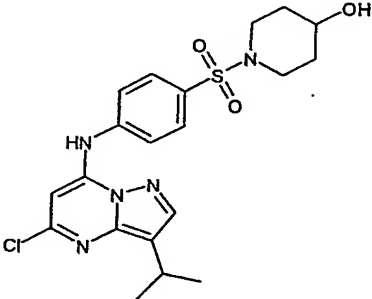
To a solution of 3-bromo-5-chloro-7-(4-(*N,N*-dimethylsulphonamido)phenylamino)pyrazolo[1,5-*a*]pyrimidine (0.05 g, 0.12 mmol) in dioxane (3 cm<sup>3</sup>) was added acetonitrile (1 cm<sup>3</sup>), 1,4-*trans*-diaminocyclohexane (0.13 g, 1.16 mmol) and triethylamine (0.08 cm<sup>3</sup>, 0.58 mmol). The reaction was heated via a microwave, in a sealed tube, at 180 °C for 2 hours. The reaction mixture was loaded onto a silica flash column and the product eluted with with 20% methanol in dichloromethane, to yield the title compound as a white solid (0.05 g, 82%).

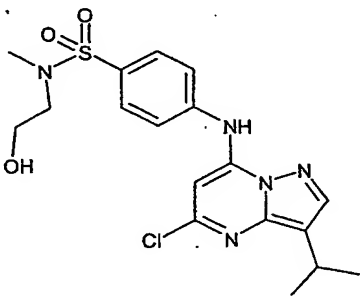
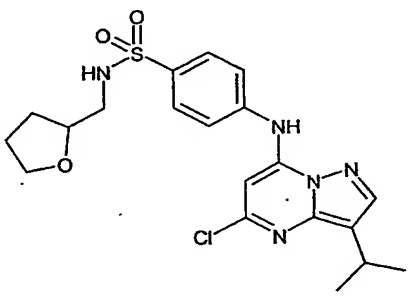
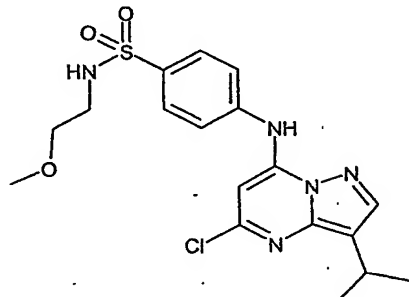
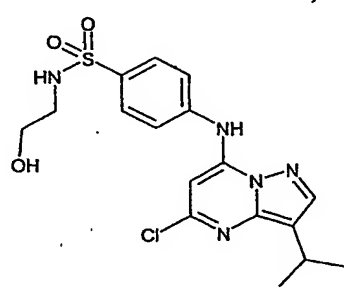
$\delta_H$  (400 MHz; d-MeOH) 7.74 (2H, d, *J* 6.7), 7.71 (1H, s), 7.52 (2H, d, *J* 6.7), 5.89 (1H, s), 3.97-3.83 (1H, m), 2.92-2.83 (1H, m), 2.12 (2H, d, *J* 10.92), 1.96 (2H, d, *J* 12.6), 1.44-1.38 (2H, m), 1.29-1.20 (2H, m).

*m/z* 510 and 512 (*M*+H, 100% and 100%), retention time 1.90 min (Method A).

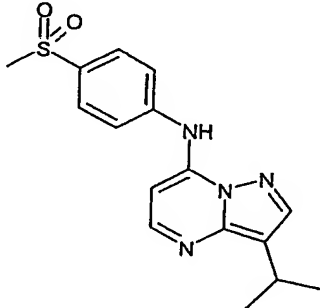
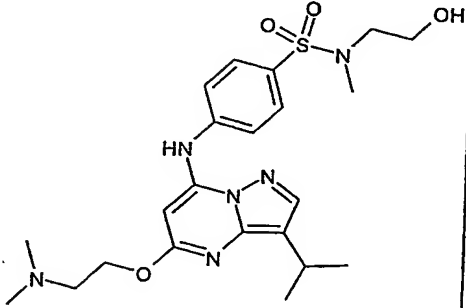
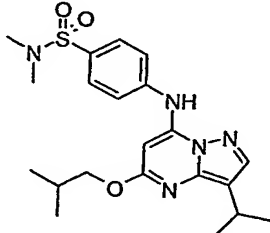
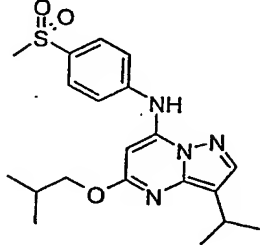
The compounds of Examples 29-31 were tested, together with additional compounds synthesised by methods analogous to those of Examples 29-31, in the assays described below in the Assay section. The result obtained in each case is given in the following Table 4.

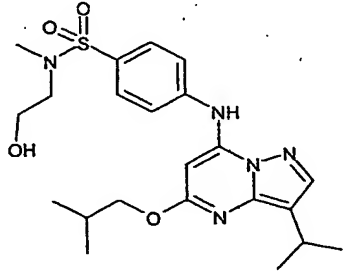
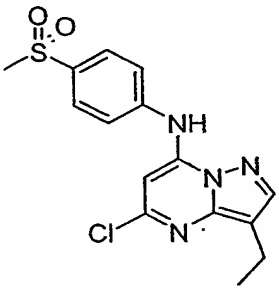
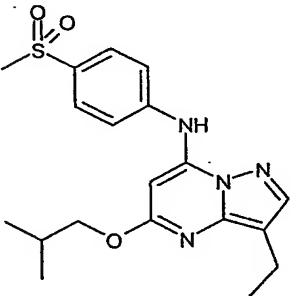
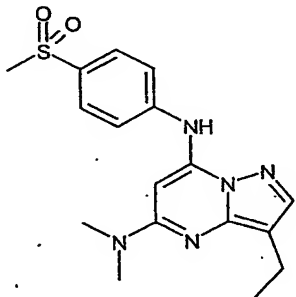
Table 4

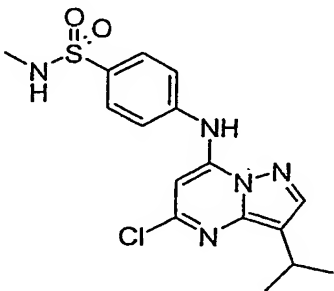
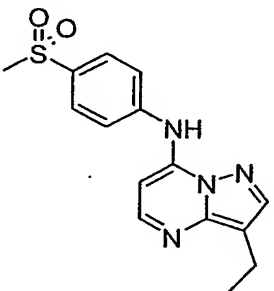
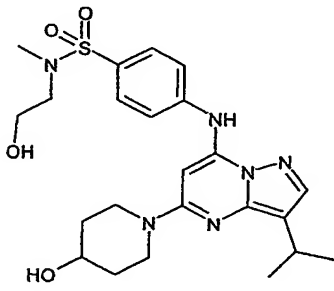
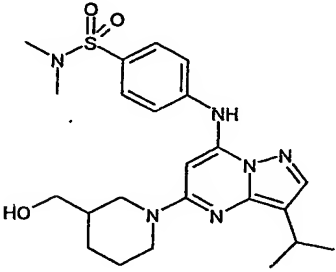
Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	m/z	RT (min)
	30	0.059	5.513	19.93 8	472 (M+H, 100%)	1.89
	31	0.008	1.269	0.325	508 and 510 (each M+H, 100%)	1.90
	32	0.062	>200	>200	366. and 368 (each M+H, 100 and 35%)	2.69
	33	0.271	>200	>200	450 and 452 (each M+H, 100 and 35%)	2.44

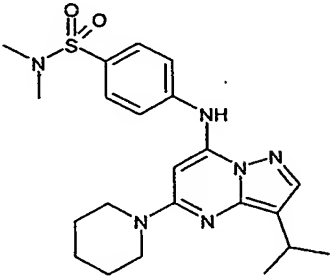
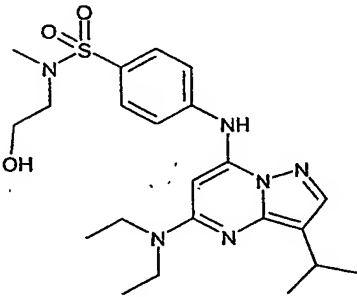
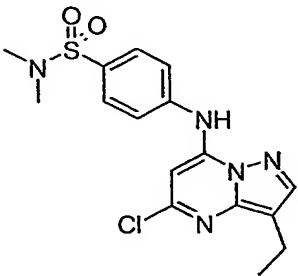
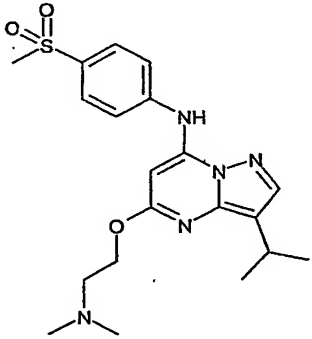
Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	m/z	RT (min)
	34	0.127	>200	>200	424 and 426 (each M+H, 100 and 35%)	2.72
	35	0.191	>200	>200	450 and 452 (each M+H, 100 and 35%)	2.87
	36	0.715	>200	>200	424 and 426 (each M+H, 100 and 35%)	2.81
	37	1.513	>200	>200	410 and 412 (each M+H, 100 and 35%)	2.61

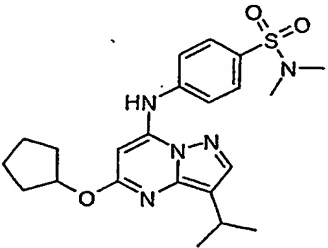
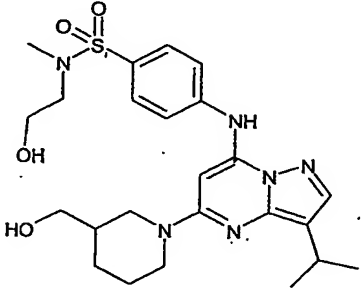
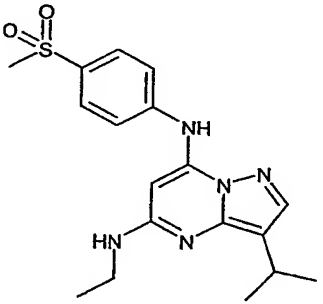
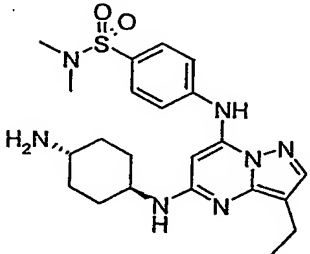


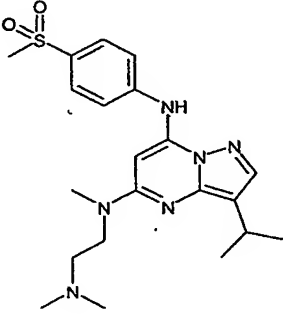
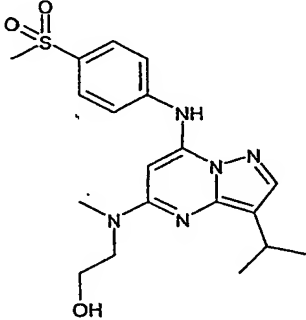
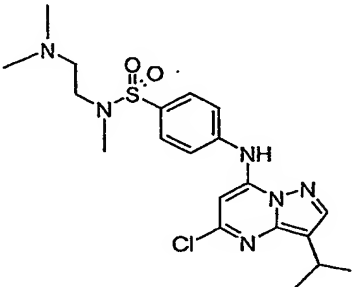
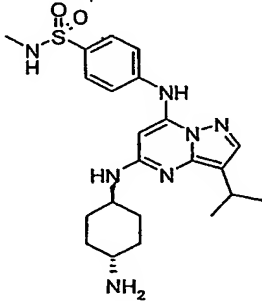
Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	m/z	RT (min)
	38	0.313	>200	>200	331 (M+H, 100%)	2.25
	39	0.403	80.76 7	>200	477 (M+H, 100%)	1.88
	40	1.164	>200	>200	432 (M+H, 100%)	3.08
	41	1.196	>200	>200	403 (M+H, 100%)	2.97

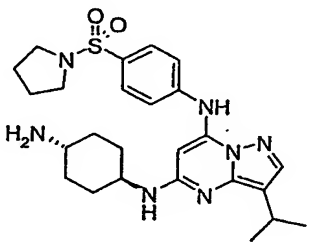
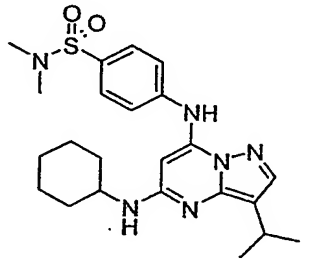
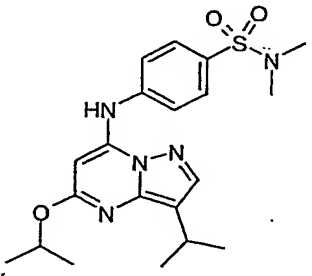
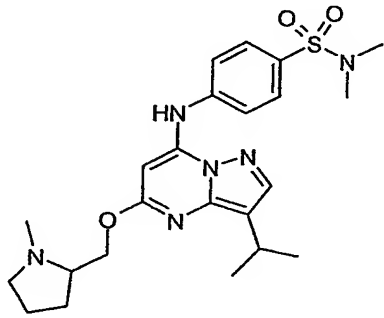
Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	m/z	RT (min)
	42	0.170	>200	>200	462 (M+H, 100%)	2.92
	43	0.107	>200	>200	351 and 353 (each M+H, 100 and 35%)	2.48
	44	0.179	>200	79.09 5	389 (M+H, 100%)	2.88
	45	1.134	>200	>200	360 (M+H, 100%)	2.43

Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	<i>m/z</i>	RT (min)
	46	0.076	>200	108.9 6	380 and 382 (each <i>M</i> + <i>H</i> , 100 and 35%)	2.64
	47	0.727	>200	>200	317 ( <i>M</i> + <i>H</i> , 100%)	2.07
	48	1.455	>200	>200	489 ( <i>M</i> + <i>H</i> , 100%)	2.31
	49	0.387	>200	>200	473 ( <i>M</i> + <i>H</i> , 100%)	2.68

Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	m/z	RT (min)
	50	1.009	>200	>200	443 (M+H, 100%)	2.98
	51	0.259	>200	>200	461 (M+H, 100%)	2.82
	52	0.239	>200	>200	380 and 382 (each M+H, 100 and 35%)	2.65
	53	8.415	>200	>200	418 (M+H, 100%)	1.87

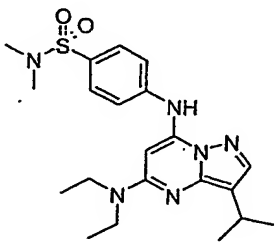
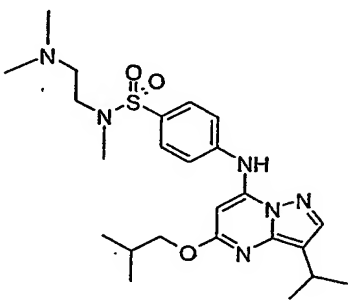
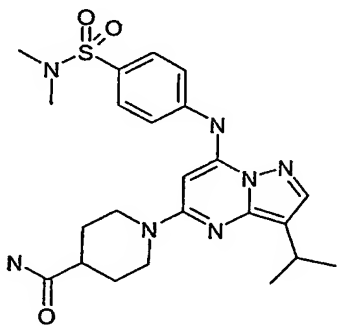
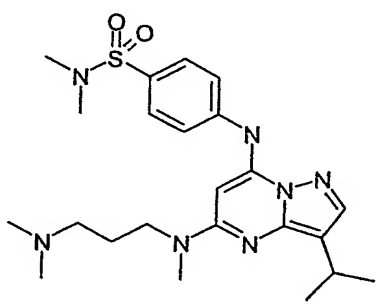
Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	m/z	RT (min)
	54	1.308	>200	>200	444 (M+H, 100%)	2.80
	55	0.270	>200	>200	503 (M+H, 100%)	2.47
	56	0.850	>200	45.33 4	374 (M+H, 100%)	2.41
	57	0.069	2.611	2.436	458 (M+H, 100%)	1.79

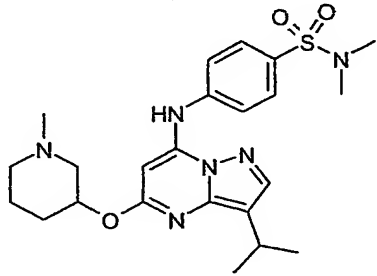
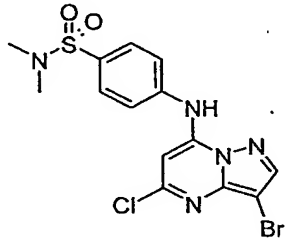
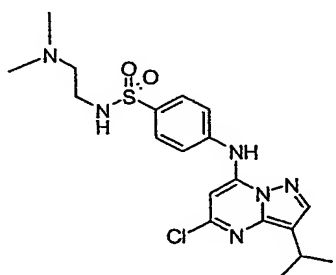
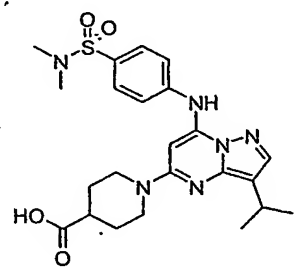
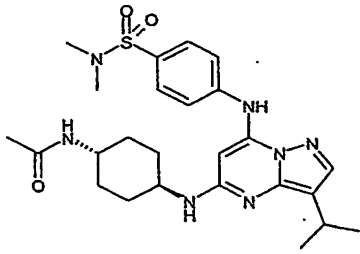
Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	m/z	RT (min)
	58	1.945	51.73 5	>200	431 (M+H, 100%)	1.87
	59	0.768	>200	>200	404 (M+H, 100%)	2.27
	60	0.040	>200	>200	451 and 453 (each M+H, 100 and 35%)	2.10
	61	0.032	6.634	11.01 5	458 (M+H, 100%)	1.83

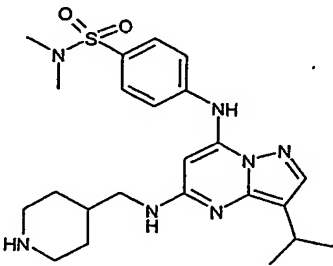
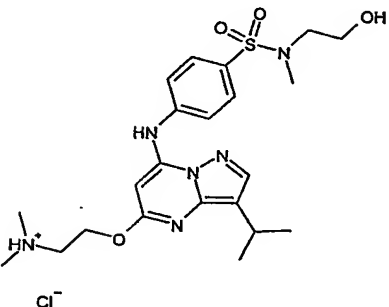
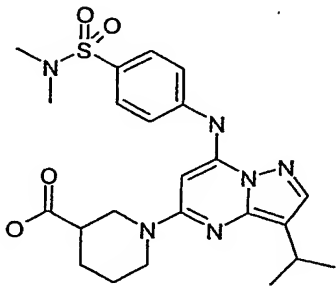
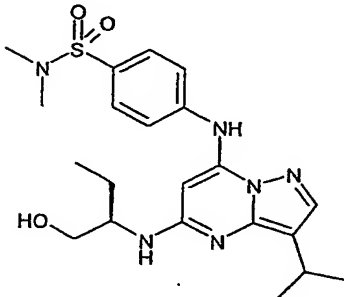
Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	<i>m/z</i>	RT (min)
	62	0.024	3.240	1.196	498 ( <i>M</i> + <i>H</i> , 100%)	2.00
	63	0.355	>200	>200	457 ( <i>M</i> + <i>H</i> , 100%)	2.97
	64	0.395	>200	>200	418 ( <i>M</i> + <i>H</i> , 100%)	3.00
	65	1.091	>200	>200	473 ( <i>M</i> + <i>H</i> , 100%)	2.06

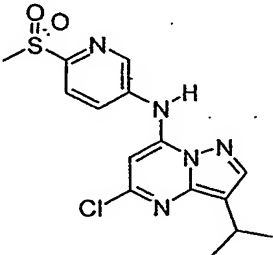
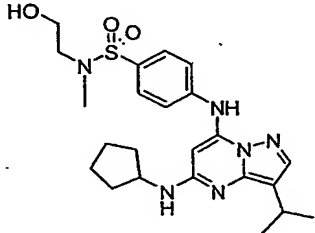
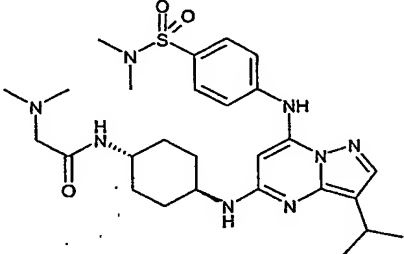
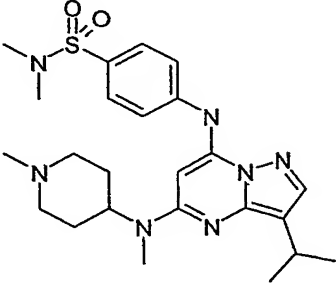
Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	m/z	RT (min)
	66	0.876	>200	>200	390 (M+H, 100%)	2.82
	67	0.030	>200	4.636	458 (M+H, 100%)	1.81
	68	0.052	>200	>200	451 and 453 (each M+H, 100 and 35%)	2.10
	69	0.181	19.25 4	31.63 0	472 (M+H, 100%)	2.00
	70	0.320	79.86 0	>200	459 (M+H, 100%)	2.03

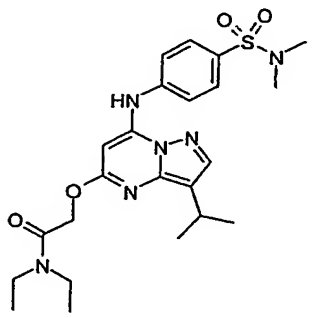
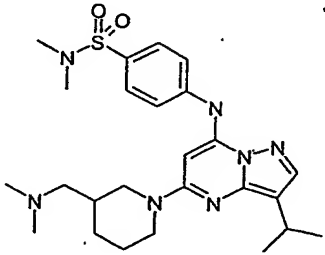
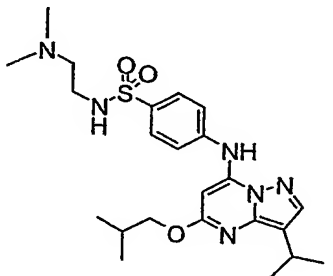
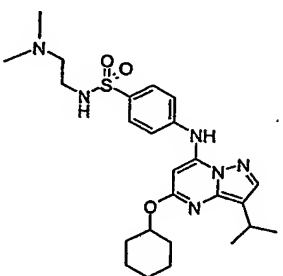


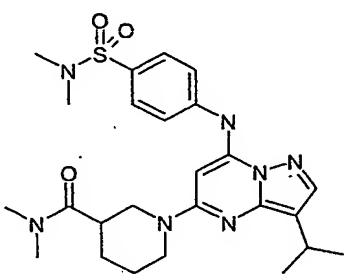
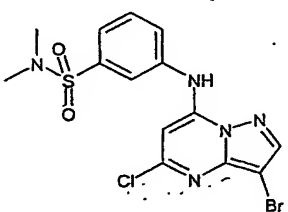
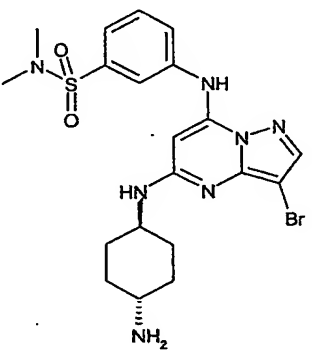
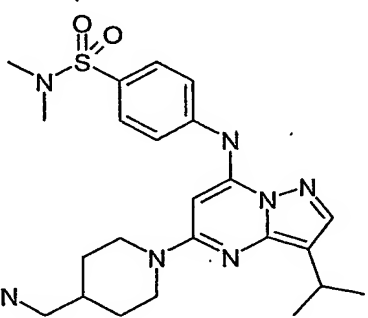
Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	<i>m/z</i>	RT (min)
	71	0.655	>200	>200	431 ( <i>M</i> + <i>H</i> , 100%)	2.96
	72	1.279	8.401	>200	489 ( <i>M</i> + <i>H</i> , 100%)	2.48
	73	1.482	>200	>200	486 ( <i>M</i> + <i>H</i> , 100%)	2.41
	74	7.275	18.55 0	>200	474 ( <i>M</i> + <i>H</i> , 100%)	2.03

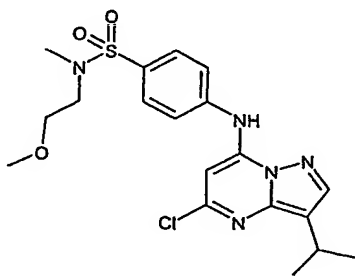
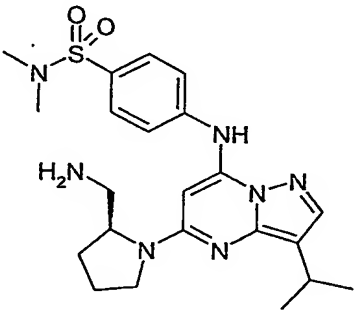
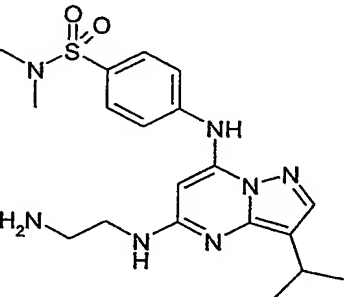
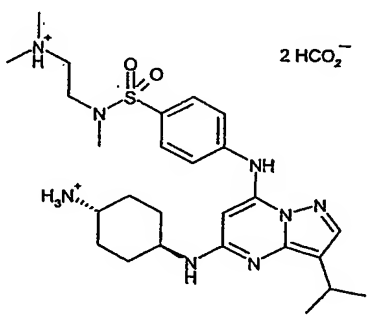
Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	m/z	RT (min)
	75	0.266	6.281	>200	473 (M+H, 100%)	2.07
	76	0.128	>200	>200	430, 432 and 434 (each M+H, 75, 100 and 25%)	2.58
	77	0.039	>200	9.491	437 and 439 (each M+H, 100 and 35%)	2.04
	78	4.786	>200	>200	487 (M+H, 100%)	2.59
	79	0.066	>200	>200	514 (M+H, 100%)	2.32

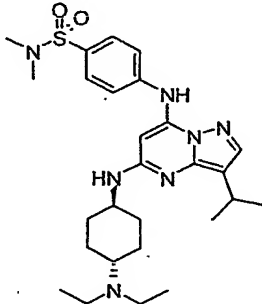
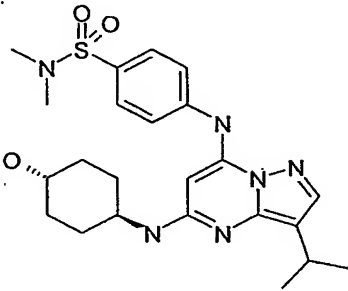
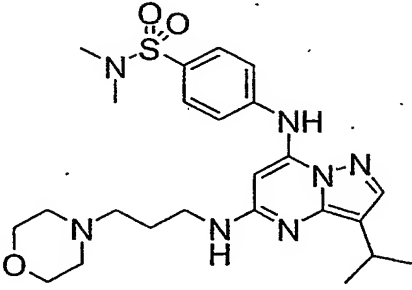
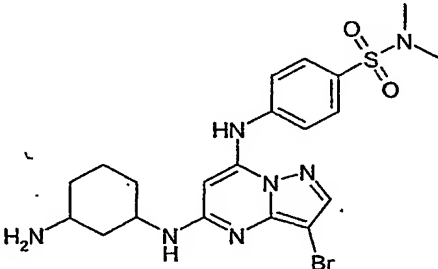
Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	m/z	RT (min)
	80	0.682	>200	2.557	472 (M+H, 100%)	1.95
 Cl <sup>-</sup>	81	0.240	46.75 3	>200	478 (M+H, 100%)	1.85
	82	4.230	>200	>200	487 (M+H, 100%)	2.58
	83	0.140	>200	>200	447 (M+H, 100%)	2.52

Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	<i>m/z</i>	RT (min)
	84	0.298	>200	>200	366 and 368 (each <i>M</i> + <i>H</i> , 100 and 35%)	2.45
	85	0.302	>200	>200	473 ( <i>M</i> + <i>H</i> , 100%)	2.73
	86	0.030	>200	>200	557 ( <i>M</i> + <i>H</i> , 100%)	1.98
	87	0.840	16.32 8	>200	486 ( <i>M</i> + <i>H</i> , 100%)	2.06

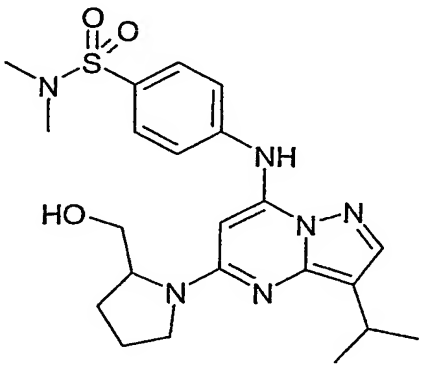
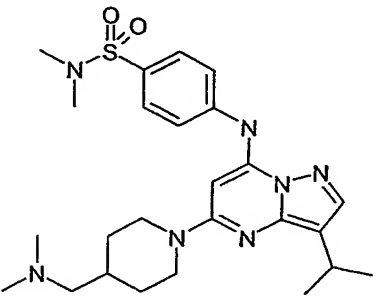
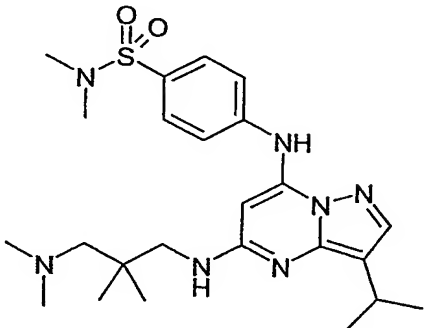
Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	<i>m/z</i>	RT (min)
	88	0.419	>200	>200	489 ( <i>M</i> + <i>H</i> , 100%)	2.68
	89	8.269	>200	>200	500 ( <i>M</i> + <i>H</i> , 100%)	2.09
	90	0.373	5.422	>200	475 ( <i>M</i> + <i>H</i> , 100%)	2.38
	91	0.881	5.358	>200	501 ( <i>M</i> + <i>H</i> , 100%)	2.56

Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	<i>m/z</i>	RT (min)
	92	10.51 3	>200	>200	514 ( <i>M</i> + <i>H</i> , 100%)	2.90
	93	0.572	>200	>200	430, 432 and 434 (each <i>M</i> + <i>H</i> , 75, 100 and 25%)	2.60
	94	0.070	27.01 0	>200	508 and 510 (each <i>M</i> + <i>H</i> , 100%)	1.81
	95	1.863	24.87 2	64.17 1	472 ( <i>M</i> + <i>H</i> , 100%)	2.05

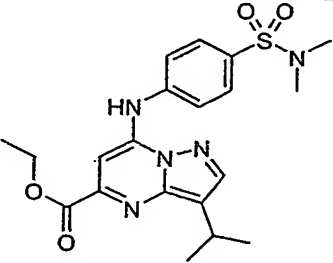
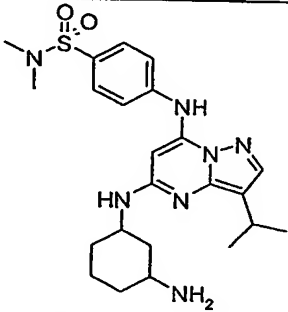
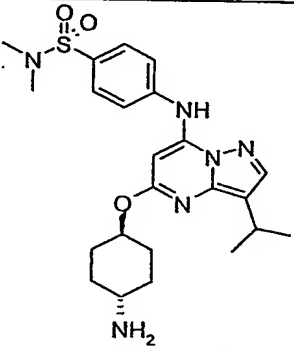
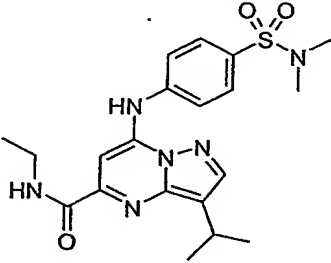
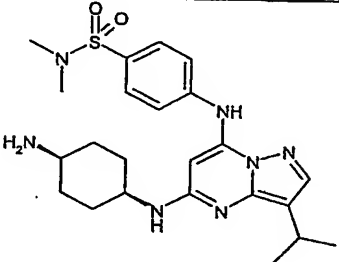
Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	m/z	RT (min)
	96	0.124	>200	>200	438 and 440 (each M+H, 100 and 35%)	2.78
	97	7.815	4.751	>200	458 (M+H, 100%)	2.00
	98	7.505	18.67 0	>200	418 (M+H, 100%)	1.91
	99	0.128	0.953	6.909	529 (M+H, 100%)	1.66

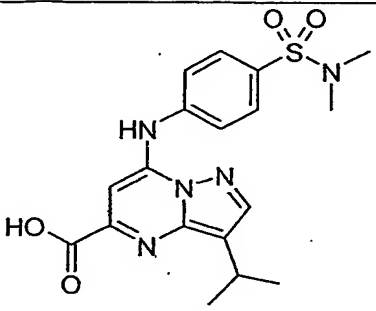
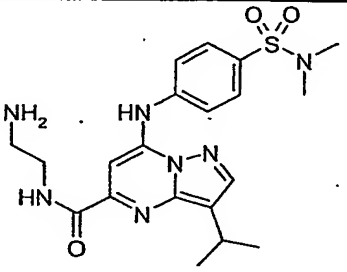
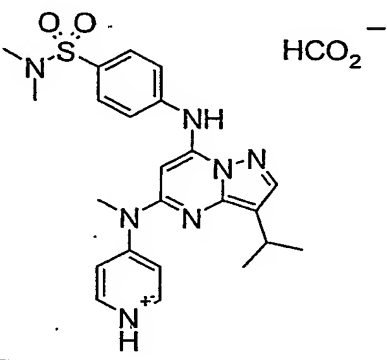
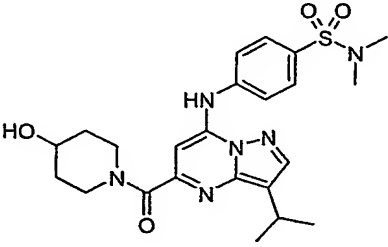
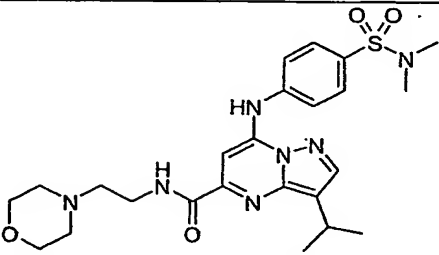
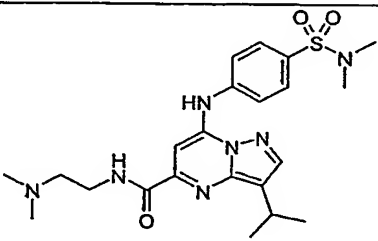
Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	<i>m/z</i>	RT (min)
	100	0.092	29.34 5	30.27 6	528 ( <i>M</i> + <i>H</i> , 100%)	2.09
	101	0.024	>200	3.812	473 ( <i>M</i> + <i>H</i> , 100%)	2.35
	102	0.965	>200	>200	502 ( <i>M</i> + <i>H</i> , 100%)	2.00
	103	0.033	0.412	27.54 9	508 and 510 (each <i>M</i> + <i>H</i> , 100%)	1.96

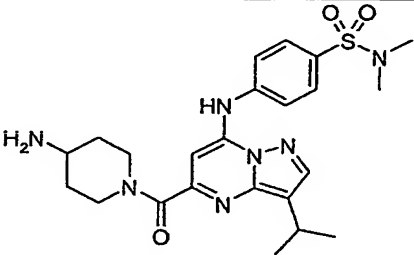
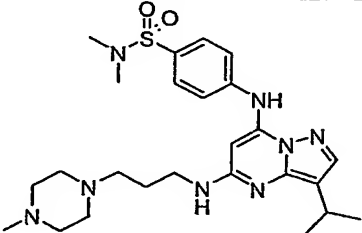
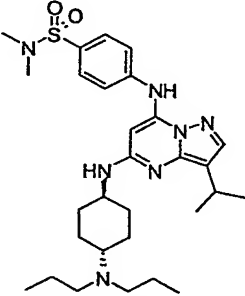
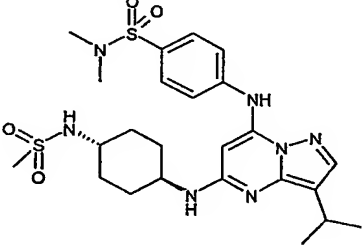
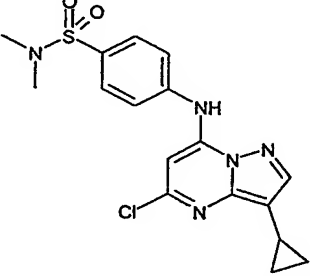
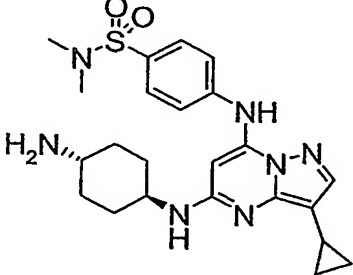


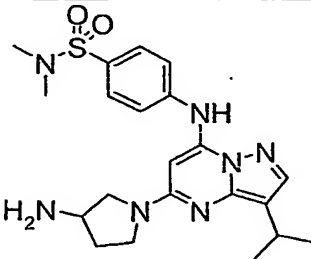
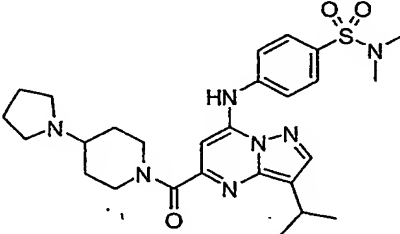
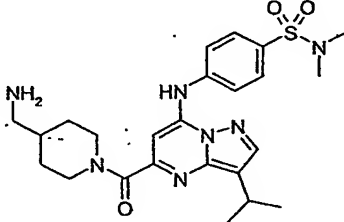
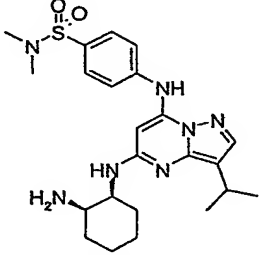
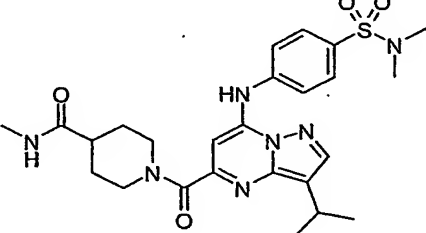
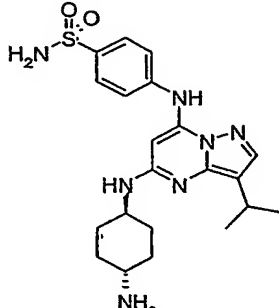
Structure	Example	CDK2 IC <sub>50</sub> ( $\mu$ M)	Chk1 IC <sub>50</sub> ( $\mu$ M)	PDK1 IC <sub>50</sub> ( $\mu$ M)	m/z	RT (min)
	104	0.177	>200	>200	459 (M+H, 100%)	2.49
	105	5.98	>200	>200	500 (M+H, 100%)	2.07
	106	3.335	18.24 6	14.40 8	488 (M+H, 100%)	2.11

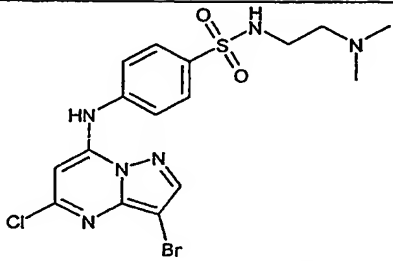
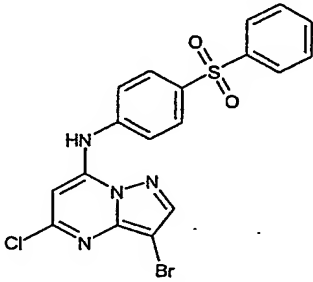
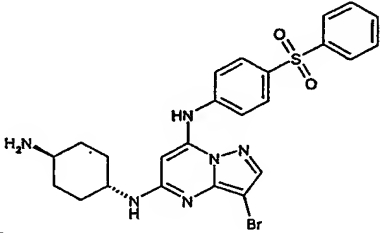
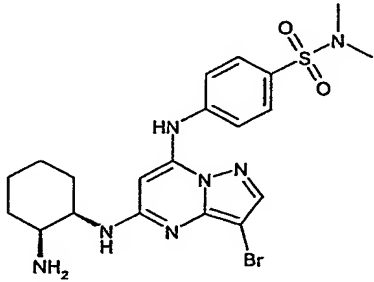
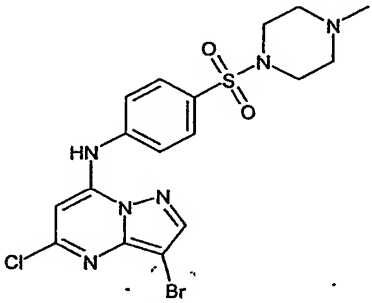
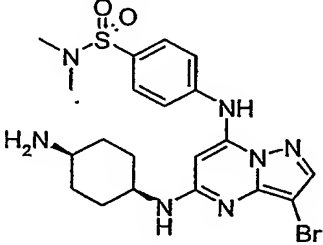
Structure	Example	CDK2 IC <sub>50</sub> (μM)	CHK1 IC <sub>50</sub> (μM)	PDK1 IC <sub>50</sub> (μM)	m/z	RT (min)
	107	0.101	19.586	96.508	444 (M+H, 100%)	1.74
	108	3.143	>200	>200	403 (M+H, 100%)	2.61
	109	10.310	15.221	>200	555 (M+H, 100%)	1.82
	110	0.305	>200	>200	543 (M+H, 100%)	2.36
	111	3.088	>200	>200	452 (M+H, 100%)	2.08

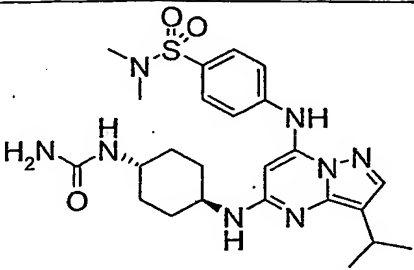
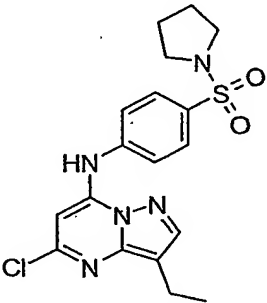
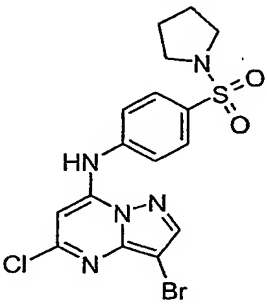
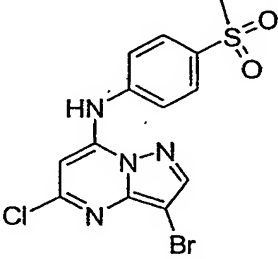
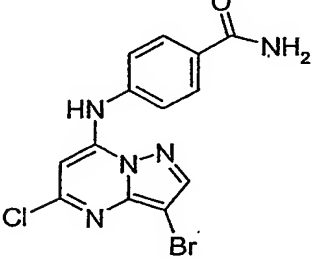
	112	0.274	>200	>200	432 (M+H, 100%)	2.69
	113	2.054	2.200	3.118	472 (M+H, 100%)	2.00
	114	0.017	3.450	125.194	473 (M+H, 100%)	2.06
	115	7.889	>200	>200	431 (M+H, 100%)	2.67
	116	0.975	2.190	0.536	472 (M+H, 100%)	2.01

	117	23.268	>200	>200	404 (M+H, 100%)	2.27
	118	6.760	36.841	>200	446 (M+H, 100%)	1.91
	119	22.674	>200	>200	466 (M+H, 100%)	2.11
	120	0.594	>200	>200	487 (M+H, 100%)	2.19
	121	9.302	>200	>200	516 (M+H, 100%)	1.96
	122	3.172	>200	>200	474 (M+H, 100%)	1.93

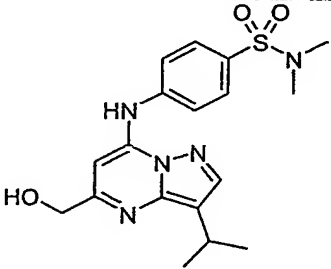
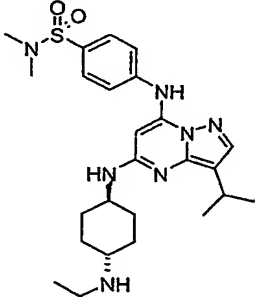
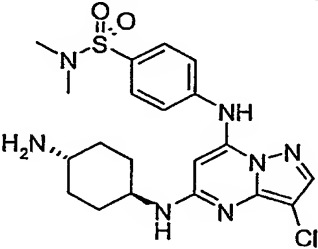
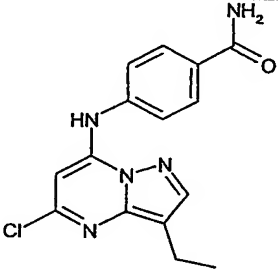
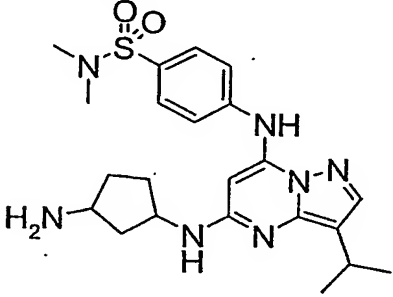
	123	1.341	>200	767.778	486 (M+H, 100%)	1.82
	124	22.076	>200	>200	515 (M+H, 100%)	1.97
	125	0.155	20.525	19.869	556 (M+H, 100%)	2.14
	126	0.073	>200	34.430	550 (M+H, 100%)	2.52
	127	0.005	>200	29.345	392 and 394 (each M+H, 100 and 35%)	2.67
	128	0.022	1.026	0.178	470 (M+H, 100%)	1.89

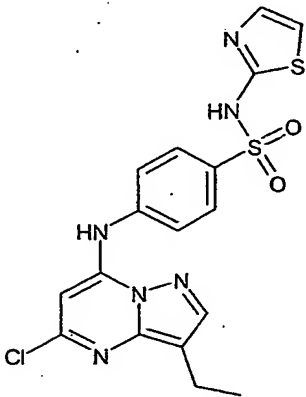
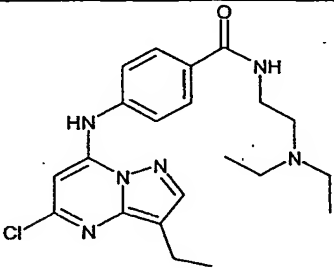
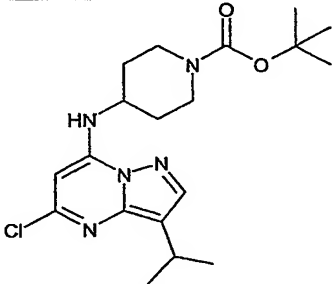
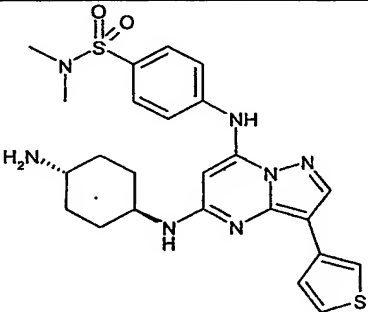
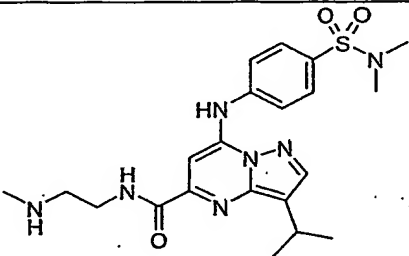
	129	1.973	ND	ND	444 (M+H, 100%)	1.95
	130	12.152	ND	ND	540 (M+H, 100%)	1.86
	131	9.368	ND	ND	500 (M+H, 100%)	1.84
	132	3.628	ND	10.371	472 (M+H, 100%)	2.10
	133	5.169	ND	ND	528 (M+H, 100%)	2.16
	134	0.026	ND	4.429	444 (M+H, 100%)	1.73

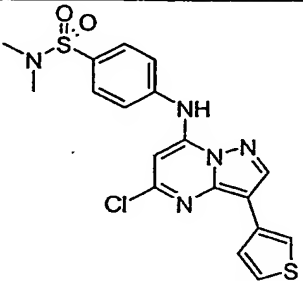
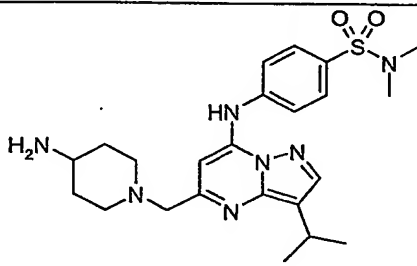
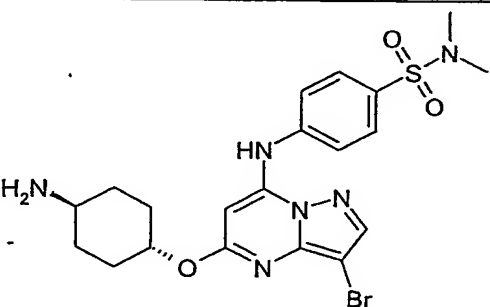
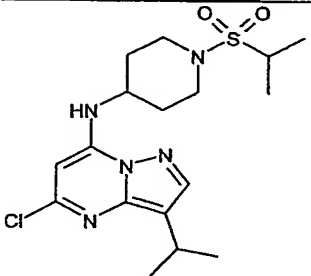
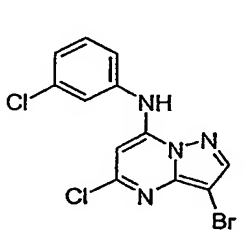
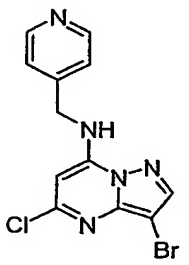
	135	0.081	ND	ND	473, 475 and 477 (each $M+H$ , 75, 100 and 25%)	1.86
	136	0.204	ND	ND	463, 465 and 467 (each $M+H$ , 75, 100 and 25%)	2.71
	137	0.016	0.717	1.057	541 and 543 (each $M+H$ , 100%)	2.00
	138	0.565	ND	ND	508 and 510 (each $M+H$ , 100%)	1.99
	139	0.176	ND	ND	485, 487 and 489 (each $M+H$ , 75, 100 and 25%)	1.96
	140	3.657	0.500	5.287	508 and 510 (each $M+H$ , 100%)	1.94

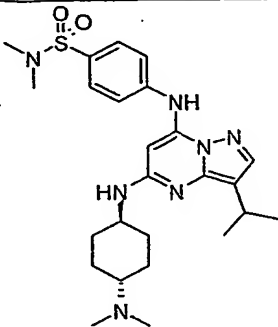
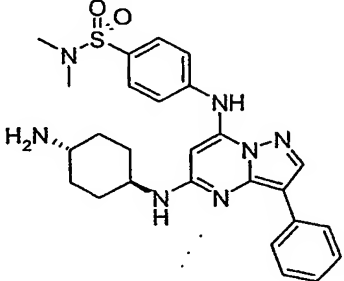
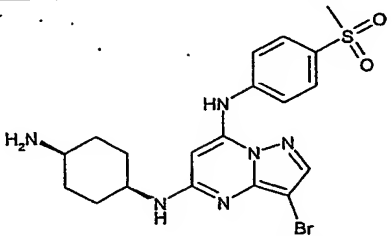
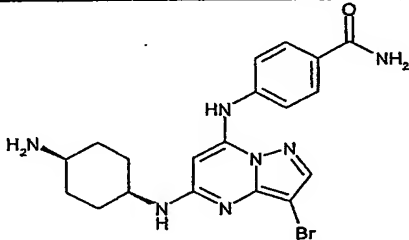
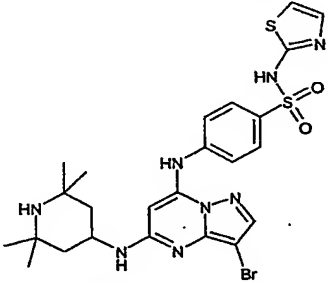
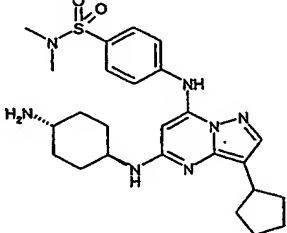
	141	0.142	ND	ND	515 (M+H, 100%)	2.18
	142	ND	ND	ND	406 and 408 (each M+H, 100 and 35%)	2.72
	143	ND	ND	ND	456, 458 and 460 (each M+H, 75, 100 and 25%)	2.65
	144	ND	ND	ND	401, 403 and 405 (each M+H, 75, 100 and 25%)	2.32
	145	ND	ND	ND	366, 368 and 370 (each M+H, 75, 100 and 25%)	2.13

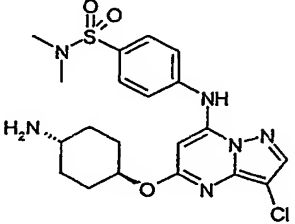
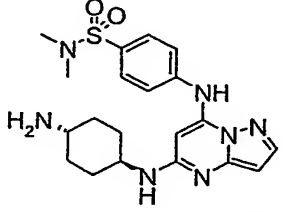
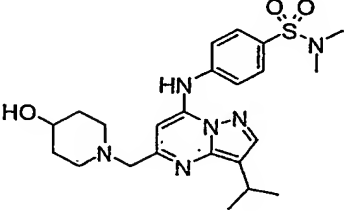
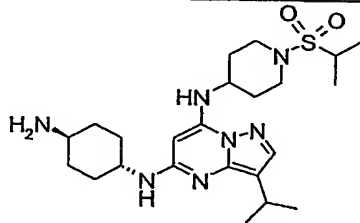
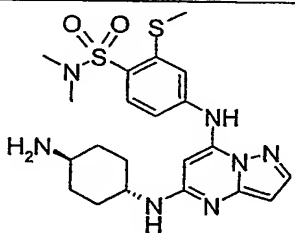
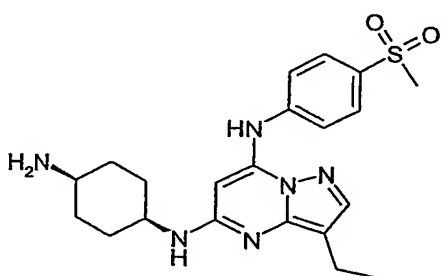
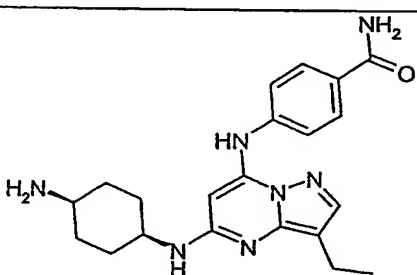


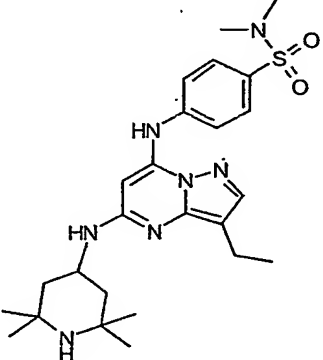
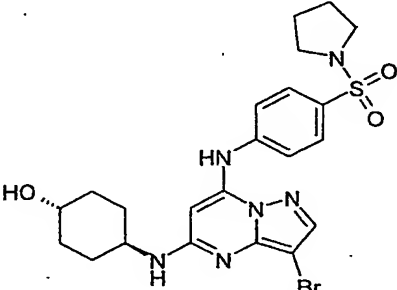
	146	0.546	ND	ND	390 ( <i>M</i> + <i>H</i> , 100%)	2.31
	147	0.098	ND	ND	500 ( <i>M</i> + <i>H</i> , 100%)	1.94
	148	0.004	ND	1.545	464 and 466 (each <i>M</i> + <i>H</i> , 100 and 35%)	1.86
	149	ND	ND	81.882	316 and 318 (each <i>M</i> + <i>H</i> , 100 and 35%)	2.21
	150	0.478	ND	ND	458 ( <i>M</i> + <i>H</i> , 100%)	1.92

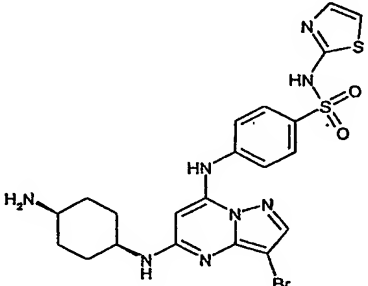
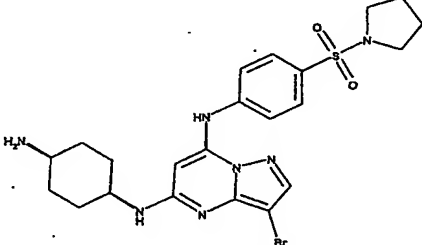
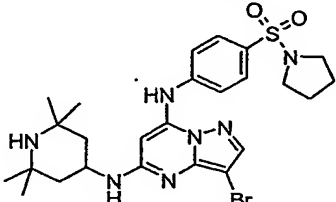
	151	ND	ND	54.454	435 and 437 (each $M+H$ , 100 and 35%)	2.38
	152	ND	ND	ND	415 and 417 (each $M+H$ , 100 and 35%)	1.92
	153	3.437	ND	ND	394 and 396 (each $M+H$ , 100 and 35%)	2.91
	154	1.421	ND	ND	512 ( $M+H$ , 100%)	2.04
	155	0.142	ND	ND	460 ( $M+H$ , 100%)	1.93

	156	24.866	ND	ND	434 and 436 (each $M+H$ , 100 and 35%)	2.78
	157	0.037	ND	ND	472 ( $M+H$ , 100%)	1.66
	158	0.005	ND	ND	509 and 511 ( $M+H$ , 100%), 531 and 533 ( $M+Na$ , 100%)	1.94
	159	1.172	ND	ND	400 and 402 ( $M+H$ , 100 and 35%)	2.70
	160	0.108	ND	ND	357, 359 and 361 (each $M+H$ , 75, 100 and 25%)	2.79
	161	0.230	ND	ND	338, 340 and 342 (each $M+H$ , 75, 100 and 25%)	1.92

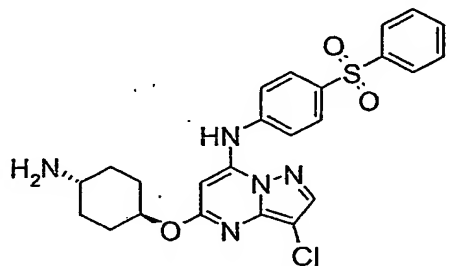
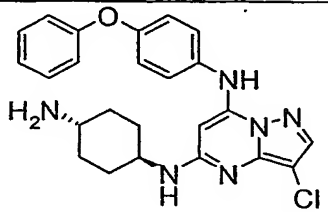
	162	0.815	ND	ND	500 ( $M+H$ , 100%)	2.01
	163	6.169	ND	ND	506 ( $M+H$ , 100%)	2.08
	164	0.222	ND	4.70	479 and 481 (each $M+H$ , 100%)	1.83
	165		ND	1.20	444 and 446 (each $M+H$ , 100%)	1.70
	166	16.859	ND	2.15	605 and 607 (each $M+H$ , 100%)	1.91
	167	0.004	ND	168.312	498 ( $M+H$ , 100%)	2.02

	168	0.014	ND	15.190	487 and 489 (M+Na, 100 and 35%)	1.90
	169	0.098	ND	3.359	430 (M+H, 100%)	1.63
	170	1.804	ND	ND	473 (M+H, 100%)	1.87
	171	11.861	ND	ND	478 (M+H, 100%)	1.73
	172	>50	ND	72.4	465 (M+H, 100%)	1.74
	173	2.173	ND	15.20	429 (M+H, 100%)	1.75
	174	ND	ND	11.28	394 (M+H, 100%)	1.62

	175	22.153	ND	12.88	500 ( <i>M</i> + <i>H</i> , 100%)	2.01
	176	0.183	ND	3.25	535 and 537 ( <i>M</i> + <i>H</i> , 100%)	2.42

Structure	Example	CDK2 IC <sub>50</sub> (μM)	Chk1 IC <sub>50</sub> (μM)	PDK1 IC <sub>50</sub> (μM)	<i>m/z</i>	RT (min)
	177	ND	ND	0.66	563 and 565 (each <i>M</i> + <i>H</i> , 100%)	1.83
	178	ND	ND	2.58	534 and 536 (each <i>M</i> + <i>H</i> , 100%)	2.00
	179	ND	ND	4.54	576 and 578 (each <i>M</i> + <i>H</i> , 100%)	2.10

Structure	Example	CDK2 IC <sub>50</sub> (μM)	Chk1 IC <sub>50</sub> (μM)	PDK1 IC <sub>50</sub> (μM)	m/z	RT (min)
	180	0.002	ND	ND	542, 544 and 546 (each <i>M</i> + <i>H</i> , 10 0, 75 and 25%)	1.97
	181	0.101	ND	ND	493 and 495 (each <i>M</i> + <i>H</i> , 100%)	2.20
	182	0.248	ND	ND	542 and 544 (each <i>M</i> + <i>H</i> , 100%)	2.48
	183	ND	ND	ND	497 and 499 (each <i>M</i> + <i>H</i> , 100 and 35%)	1.97
	184	ND	ND	ND	564 and 566 (each <i>M</i> + <i>H</i> , 100%)	2.06
	185	ND	ND	ND	538 and 540 (each <i>M</i> + <i>H</i> , 100%)	1.91

	186	ND	ND	ND	520 and 522 (each <i>M</i> + <i>H</i> , 100 and 35%)	2.05
	187	ND	ND	ND	449 and 451 (each <i>M</i> + <i>H</i> , 100 and 35%)	2.18

In the above Table "ND" means the compound was not tested in that assay.

#### Assay Conditions:

##### CDK2

Assays for the cyclin dependent kinase activity were carried out by monitoring the phosphorylation of a synthetic peptide, HATTPKKRK. The assay mixture containing the inhibitor and CDK-2 enzyme, complexed with cyclin A (0.4U/ml) was mixed together in a microtiter plate in a final volume of 50 $\mu$ l and incubated for 40 min at 30°C. The assay mixture contained 0.1 mM unlabeled ATP, 0.01 $\mu$ Ci/ $\mu$ l  $^{33}$ P- $\gamma$ -ATP, 0.03mM peptide, 0.1mg/ml BSA, 7.5mM magnesium acetate, 50mM HEPES-NaOH, pH 7.5. The reaction was stopped by adding 50 $\mu$ l of 50mM phosphoric acid. 90 $\mu$ l of the mixture were transferred to a pre-wetted 96-well Multiscreen MAPHNOB filtration plate (Millipore) and filtered on a vacuum manifold. The filter plate was washed with 3 successive additions of 200 $\mu$ l 50mM phosphoric acid and then with 100 $\mu$ l methanol. The filtration plate was dried for 10 min at 65°C, scintillant added and phosphorylated peptide quantified in a scintillation counter (Trilux, PerkinElmer)

HEPES is N-[2-Hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]

BSA is bovine serum albumin.



PDK1

Assays for the PDK dependent kinase activity were carried out by monitoring the phosphorylation of a synthetic peptide, KTFCGTPEYLAPEVRREPRILSEEEQEMFRDFDYIADWC. The assay mixture containing the inhibitor and PDK1 enzyme was mixed together in a microtiter plate in a final volume of 50 $\mu$ l and incubated for 60 min at 30°C. The assay mixture contained 0.01 mM unlabeled ATP, 0.01 $\mu$ Ci/ $\mu$ l  $^{33}$ P- $\gamma$ -ATP, 0.075mM peptide, 0.1mg/ml BSA, 7.5mM magnesium acetate, 0.05M Tris.HCl, pH 7.5, 0.5% 2-mercaptoethanol. The reaction was stopped by adding 50 $\mu$ l of 50mM phosphoric acid. 90 $\mu$ l of the mixture were transferred to a pre-wetted 96-well Multiscreen MAPHNOB filtration plate (Millipore) and filtered on a vacuum manifold. The filter plate was washed with 3 successive additions of 200 $\mu$ l 50mM phosphoric acid and then with 100 $\mu$ l methanol. The filtration plate was dried for 10 min at 65°C, scintillant added and phosphorylated peptide quantified in a scintillation counter (Trilux, PerkinElmer)

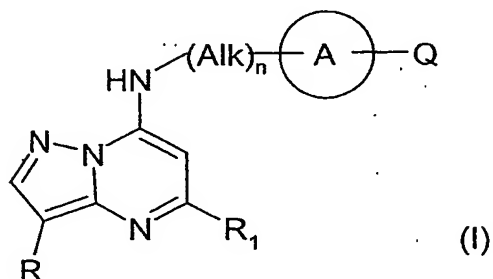
CHK1:

Assays for the Chk1 kinase activity were carried out by monitoring the phosphorylation of a synthetic peptide Chktide with the amino acid sequence, KKKVSRSGLYRSPSPENLNRPR. The assay mixture containing the inhibitor and Chk1 enzyme was mixed together in a microtiter plate in a final volume of 50 $\mu$ l and incubated for 40 minutes at 30°C.

The assay mixture contained 0.01mM unlabeled ATP, 0.5 $\mu$ Ci  $^{33}$ P- $\gamma$ -ATP, 30 $\mu$ M Chktide, 0.1mg/ml BSA, 50mM Hepes-NaOH pH 7.5 and 11nM GST-Chk1 enzyme. The reaction was stopped by adding 50 $\mu$ l of 50mM phosphoric acid. 90 $\mu$ l of the mixture was transferred to a pre-wetted 96-well Multiscreen MAPHNOB filtration plate (Millipore) and filtered on a vacuum manifold. The filter plate was washed with 3 successive additions of 200 $\mu$ l 50mM phosphoric acid and then with 100 $\mu$ l methanol. The filtration plate was dried for 10 min at 65°C, scintillant added and phosphorylated peptide quantified in a scintillation counter (Trilux, PerkinElmer)

# Claims.

1. The use of a compound of formula (I) or a salt, N-oxide, hydrate or solvate thereof, in the preparation of a composition for inhibition of kinase activity:



wherein

Ring A is an optionally substituted carbocyclic or heterocyclic radical,

Alk represents an optionally substituted divalent C<sub>1</sub>-C<sub>6</sub> alkylene radical;

n is 0 or 1;

Q represents a radical of formula  $-(\text{Alk}^1)_p-(\text{X})_r-(\text{Alk}^2)_s-\text{Z}$  wherein in any compatible combination

Z is hydrogen or an optionally substituted carbocyclic or heterocyclic ring,

Alk<sup>1</sup> and Alk<sup>2</sup> are optionally substituted divalent C<sub>1</sub>-C<sub>6</sub> alkylene radicals which may contain a -O-, -S- or -NR<sup>A</sup>- link, wherein R<sup>A</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl,

X represents -O-, -S-, -(C=O)-, -(C=S)-, -SO<sub>2</sub>-, -SO-, -C(=O)O-, -OC(=O)-, -C(=O)NR<sup>A</sup>-, -NR<sup>A</sup>C(=O)-, -C(=S)NR<sup>A</sup>-, -NR<sup>A</sup>C(=S)-, -SO<sub>2</sub>NR<sup>A</sup>-, -NR<sup>A</sup>SO<sub>2</sub>-, -OC(=O)NR<sup>A</sup>-, -NR<sup>A</sup>C(=O)O-, or -NR<sup>A</sup>- wherein R<sup>A</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl, and

p, r and s are independently 0 or 1,

$R_1$  represents a radical  $-(Alk^3)_a-(Y)_b-(Alk^4)_d-B$  wherein  
a, b and d are independently 0 or 1,

$Alk^3$  and  $Alk^4$  are optionally substituted divalent  $C_1$ - $C_3$  alkylene radicals,

Y represents a monocyclic divalent carbocyclic or heterocyclic radical  
having from 5 to 8 ring atoms, -O-, -S-, or  $-NR^A$ - wherein  $R^A$  is  
hydrogen or  $C_1$ - $C_6$  alkyl,

B represents hydrogen or halo, or an optionally substituted monocyclic  
carbocyclic or heterocyclic ring having from 5 to 8 ring atoms, or in the  
case where Y is  $-NR^A$ - and b is 1, then  $R^A$  and the radical  $-(Alk^4)_d-B$   
taken together with the nitrogen to which they are attached may form  
an optionally substituted heterocyclic ring,

R represents hydrogen, halo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkylthio,  
phenyl, benzyl, cycloalkyl with 3 to 6 ring atoms, or a monocyclic heterocyclic  
group having 5 or 6 ring atoms.

2. The use as claimed in claim 1 wherein ring A is an optionally substituted monocyclic aryl or heteroaryl radical.
3. The use as claimed in claim 2 wherein ring A is phenyl, naphthyl, 2-, 3- and 4-pyridyl, 5-pyrimidinyl, 2- and 3-thienyl, 2- and 3-furyl, piperazinyl, pyrrolidinyl, or thiazolinyl.
4. The use as claimed in claim 1 wherein ring A is phenyl.
5. The use as claimed in any of the preceding claims wherein ring A is unsubstituted or substituted by methyl, ethyl, methylenedioxy, ethylenedioxy, methoxy, ethoxy, methylthio, ethylthio, hydroxy, hydroxymethyl, hydroxyethyl, mercapto, mercaptomethyl, mercaptoethyl, amino, mono- or di-methylamino,

mono- or di-ethylamino, fluoro, chloro, bromo, cyano, N-morpholino, N-piperidinyl, or N-piperazinyl, the latter being optionally C<sub>1</sub>-C<sub>6</sub> alkyl- or benzyl-substituted on the free ring nitrogen, dimethylaminosulfonyl, phenylsulfonyl or phenoxy.

6. The use as claimed in any of claims 1 to 3 wherein Q is hydrogen and the ring A is 4-(dimethylaminosulfonyl)-phenyl, 4-(phenylsulfonyl)-phenyl, 4-(phenoxy)-phenyl, 3-chloro-4-(dimethylaminosulfonyl)-phenyl, 3-chloro-4-(phenylsulfonyl)-phenyl, 3-chloro-4-(phenoxy)-phenyl, 3-methoxy-4-(dimethylaminosulfonyl)-phenyl, 3-methoxy-4-(phenylsulfonyl)-phenyl, or 3-methoxy-4-(phenoxy)-phenyl.

7. The use as claimed in any of claims 1 to 5 wherein n is 1 and Alk is —CH<sub>2</sub>—, —CH<sub>2</sub>CH<sub>2</sub>—, —CH<sub>2</sub>CH(CH<sub>3</sub>)—, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>—, —CH=CH—, —CH<sub>2</sub>CH=CH—, —CH<sub>2</sub>CH=CHCH<sub>2</sub>—, —CH=CHCH=CH—, —C≡C—, —CH<sub>2</sub>C≡C—, or —CH<sub>2</sub>C≡CCH<sub>2</sub>—.

8. The use as claimed in any of claims 1 to 5 wherein n is 1 and Alk is —CH<sub>2</sub>—.

9. The use as claimed in any of claims 1 to 5 wherein n is 0.

10. The use as claimed in any of claims 1 to 5 wherein each of p, r and s is 0, and Z is hydrogen.

11. The use as claimed in any of claims 1 to 5 wherein p, r and s are each 0, and Z is an optionally substituted monocyclic carbocyclic or heterocyclic ring.

12. The use as claimed in claim 11 wherein Z is an optionally substituted phenyl, cyclopentyl, cyclohexyl, pyridyl, morpholino, piperidinyl, or piperazyl ring.

13. The use as claimed in any of claims 1 to 5 wherein one or more of p, r and s is 1, and Z is hydrogen or an optionally substituted monocyclic carbocyclic or heterocyclic ring.
14. The use as claimed in claim 13 wherein p and/or s are each 1 and r is 0
15. The use as claimed in claim 13 wherein each of p, r, and s is 1.
16. The use as claimed in claim 13 wherein p and s are each 0 and r is 1.
17. The use as claimed in claim 16 wherein X is  $-\text{SO}_2-$ ,  $-\text{O}-$ , a sulfonamide radical  $-\text{NR}^{\text{A}}\text{SO}_2-$  or a carboxamide radical  $-\text{NR}^{\text{A}}\text{C}(=\text{O})-$  with the N atom linked to the ring A.
18. The use as claimed in claim 13 wherein p is 0, r is 1, s is 1 or 0, and X is a sulfonamide radical  $-\text{NR}^{\text{A}}\text{SO}_2-$  or a carboxamide radical  $-\text{NR}^{\text{A}}\text{C}(=\text{O})-$  with the N atom linked to the ring A.
19. The use as claimed in claim 17 or claim 18 wherein  $\text{R}^{\text{A}}$  is hydrogen or methyl.
20. The use as claimed in claim 18 or claim 19 wherein s is 1 and Z is hydrogen.
21. The use as claimed in claim 18 or claim 19 wherein s is 0 and Z is an optionally substituted monocyclic carbocyclic or heterocyclic ring.
22. The use as claimed in claim 21 wherein Z is optionally substituted phenyl.
23. The use as claimed in any of the preceding claims wherein in the radical  $\text{R}_1$  a, b and d are all 0.

24. The use as claimed in any of claims 1 to 22 wherein in the radical  $R_1$  a and d are each 0 and b is 1.

25. The use as claimed in any of claims 1 to 22 wherein in the radical  $R_1$  b is 0 and at least one of a and d is 1.

26. The use as claimed in any of claims 23 to 25 wherein in the radical  $R_1$ , B is an optionally substituted monocyclic carbocyclic or heterocyclic ring.

27. The use as claimed in claim 26 wherein B is an optionally substituted cyclopentyl, cyclohexyl, phenyl, 2-,3-, or 4-pyridyl, 2-, or 3-thienyl, 2-, or 3-furanyl, pyrrolyl, pyranal, or piperidinyl ring.

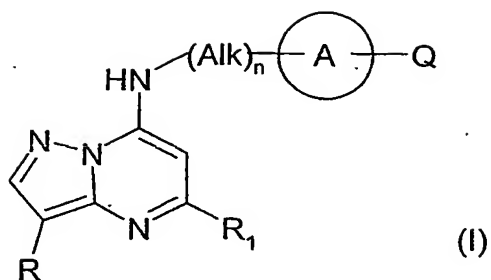
28. The use as claimed in claim 27 wherein optional substituents are selected from methyl, ethyl, methoxy, ethoxy, methylenedioxy, ethylenedioxy, methylthio, ethylthio, hydroxy, hydroxymethyl, hydroxyethyl, mercapto, mercaptomethyl, mercaptoethyl, amino, mono- and di-methylamino, mono- and di-ethylamino, fluoro, chloro, bromo, cyano, N-morpholino, N-piperidinyl, N-piperazinyl.

29. The use as claimed in any of claims 1 to 22 wherein  $R_1$  is optionally substituted cyclohexyloxy; cyclohexylamino; cyclohexylmethyl, or piperidin-1-ylmethyl.

30. The use as claimed in any of claims 1 to 22 wherein  $R_1$  is 4-aminocyclohexyloxy; 4-aminocyclohexylamino; 4-hydroxycyclohexylamino, 4-aminocyclohexylmethyl, or 4-aminopiperidin-1-ylmethyl.

31. The use as claimed in any of the preceding claims wherein R is hydrogen, chloro, bromo methyl, ethyl, n-propyl, iso-propyl, n-, sec- or tert-butyl, methoxy, methylthio, ethoxy, ethylthio, or a phenyl, benzyl, cyclopropyl, cyclopentyl, cyclohexyl, 2-, 3-, or 4- pyridyl, phenyl, pyridyl, morpholino, piperidinyl, or piperazyl ring.

32. The use as claimed in any of claims 1 to 30 wherein R is chloro, bromo, cyclopentyl, cyclopropyl or isopropyl.
33. The use as claimed in claim 1 wherein in the compound of formula (I) n is 0, ring A is optionally substituted phenyl, Q is dimethylaminosulfonyl, phenylsulfonyl or phenoxy; R<sup>1</sup> is 4-aminocyclohexyloxy, 4-aminocyclohexylamino, 4-hydroxycyclohexylamino, 4-aminocyclohexylmethyl, or 4-aminopiperidin-1-ylmethyl, and R is chloro, bromo, cyclopentyl, cyclopropyl or isopropyl.
34. A method of treatment of diseases or conditions mediated by excessive or inappropriate kinase activity in mammals, particularly humans, which method comprises administering to the mammal an amount of a compound of formula (I) as defined in any of the preceding claims, or a salt, hydrate or solvate thereof, effective to inhibit said kinase activity.
35. A compound of formula (I) as defined in any of claims 1 to 33, or a salt hydrate or solvate thereof, for use in human or veterinary medicine, particularly in the treatment of diseases or conditions mediated by excessive or inappropriate kinase activity.
- 36.. The use as claimed in any of claims 1 to 33, a method as claimed in claim 34, or a compound for use as claimed in claim 35, wherein the kinase activity is CDK2 and/or PDK1 and/or CHK1 activity.
37. The use as claimed in any of claims 1 to 33, a method of treatment as claimed in claim 34, or a compound for use as claimed in claim 35 wherein the kinase activity is associated with cancer, psoriasis or restenosis.
38. A compound of formula (I) as defined in any of claims 1 to 32, or a salt, N-oxide, hydrate or solvate thereof.
39. A compound of formula (I), or a salt, N-oxide, hydrate or solvate thereof,



wherein n is 0, ring A is optionally substituted phenyl, Q is dimethylaminosulfonyl, phenylsulfonyl or phenoxy, R<sup>1</sup> is 4-aminocyclohexyloxy; 4-aminocyclohexylamino; 4-hydroxycyclohexylamino; 4-aminocyclohexylmethyl, or 4-aminopiperidin-1-ylmethyl, and R is chloro, bromo, cyclopentyl, cyclopropyl or isopropyl.

40 A pharmaceutical composition as claimed in claim 38 or claim 39 together with a pharmaceutically acceptable carrier.



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